National Toxicology Program

U.S. Department of Health and Human Services

Annual Report 2009

National Toxicology Program

ANNUAL REPORT
For
Fiscal Year 2009

National Institute of Environmental Health Sciences
National Institutes of Health

National Center for Toxicological Research
Food and Drug Administration

National Institute for Occupational Safety and Health
Centers for Disease Control and Prevention

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National Toxicology Program
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Frequently Used Abbreviations

ACB	allele-specific competitive blocker
ACVP	American College of Veterinary Pathologists
ADME	absorption, distribution, metabolism, and excretion
AHS	Agricultural Health Study
ATSDR	Agency for Toxic Substances and Disease Registry
AZT	zidovudine
BCOP	Bovine Corneal Opacity and Permeability
BPA	bisphenol A
BrdU	bromodeoxyuridine
BSC	Board of Scientific Counselors
CASRN	CAS Registry Number
CDC	Centers for Disease Control and Prevention
CERHR	Center for the Evaluation of Risks to Human Reproduction
CNT	carbon nanotube
COX	cyclooxygenase
CPSC	U.S. Consumer Product Safey Commission
Cr(VI)	hexavalent chromium
CYP	cytochrome P450
DA	Daicel adenosine triphosphate
DEHP	di(2-ethylhexyl) phthalate
DEP	diesel exhaust particles
DHHS	Department of Health and Human Services
DTBBA	dithiobisbenzanilide
ECVAM	European Centre for the Validation of Alternative Methods
EGEHE	ethylene glycol 2-ethylhexyl ether
ELISA	enzyme-linked immunosorbent assay
EPA	Environmental Protection Agency
ER	estrogen receptor
FDA	Food and Drug Administration
FY	fiscal year
GABA	gamma-aminobutyric acid
GC/MS	gas chromatography/mass spectroscopy
GMM	genetically modified model
HHE	Health Hazard Evaluations
HTS	high throughput screening
IAG	interagency agreement
IARC	International Agency for Research on Cancer
ICATM	International Cooperation on Alternative Test Methods
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
ICE	Isolated Chicken Eye
IgE	immunoglobulin E
JaCVAM	Japanese Center for the Validation of Alternative Methods
LC/MS/MS	liquid chromatography/tandem mass spectrometry
LLNA	Local Lymph Node Assay
MDIG	mineral dust-induced gene
MIE-NN	mutual information expansion-nearest neighbor
Mn	manganese

MOC	Memorandum of Cooperation
MOU	Memorandum of Understanding
MS	mass spectrometry
MWF	metal working fluid
NCGC	NIH Chemical Genomics Center
NCI	National Cancer Institute
NCTR	National Center for Toxicological Research
NHGRI	National Human Genome Research Institute
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
NIEHS	National Institute of Environmental Health Sciences
NIH	National Institutes of Health
NIOSH	National Institute for Occupational Safety and Health
NMDA	*N*-methyl-D-aspartic acid
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OPA	orthophthalaldehyde
OSHA	Occupational Safety and Health Administration
PBPK	physiologically based pharmacokinetic
PBPK/PD	PBPK/pharmacodynamic
PCBTF	chloro-4-(trifluoromethyl) benzene
PCR	polymerase chain reaction
PPAR	peroxisome proliferator-activated receptor
qHCS	quantitative high-content screens
qHTS	quantitative high throughput screens
RACB	reproductive assessment by continuous breeding
RoC	Report on Carcinogens
ROS	reactive oxygen species
RPT	rabbit pyrogen test
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SOT	Society of Toxicology
STP	Society of Toxicologic Pathologists
SULT1A1	sulfotransferase 1A1
SWCNT	single-walled carbon nanotube
TDI	toluene diisocyanate
TiO_2	titanium dioxide
TR	Technical Report
TRRS	Technical Reports Review Subcommittee
TZD	glitazones
UV	ultraviolet
U.S.	United States
WC-Co	tungsten carbide-cobalt

Letter from the NIEHS/NTP Director

I became Director of the National Institute of Environmental Health Sciences (NIEHS) and National Toxicology Program (NTP) in January 2009, after serving for many years as director of the Experimental Toxicology Division at the U.S. Environmental Protection Agency (EPA). With my leadership, the NTP's strength continues to be the collective activities of its agency partners – the Centers for Disease Control and Prevention/National Institute for Occupational Safety and Health (CDC/NIOSH), the Food and Drug Administration/National Center for Toxicological Research (FDA/NCTR), and the National Institutes of Health/NIEHS.

One of my first accomplishments was to establish, with my counterparts in Japan, Europe, and Canada, the International Cooperation on Alternative Test Methods (ICATM), which promotes enhanced international cooperation and coordination of the scientific validation of alternative toxicity testing methods that will reduce, refine, and/or replace animal use for regulatory testing. Our commitment to alternative methods continues with the interagency agreement with the National Human Genome Research Institute's NIH Chemical Genomics Center and the EPA's National Center for Computational Toxicology ToxCast™ program.

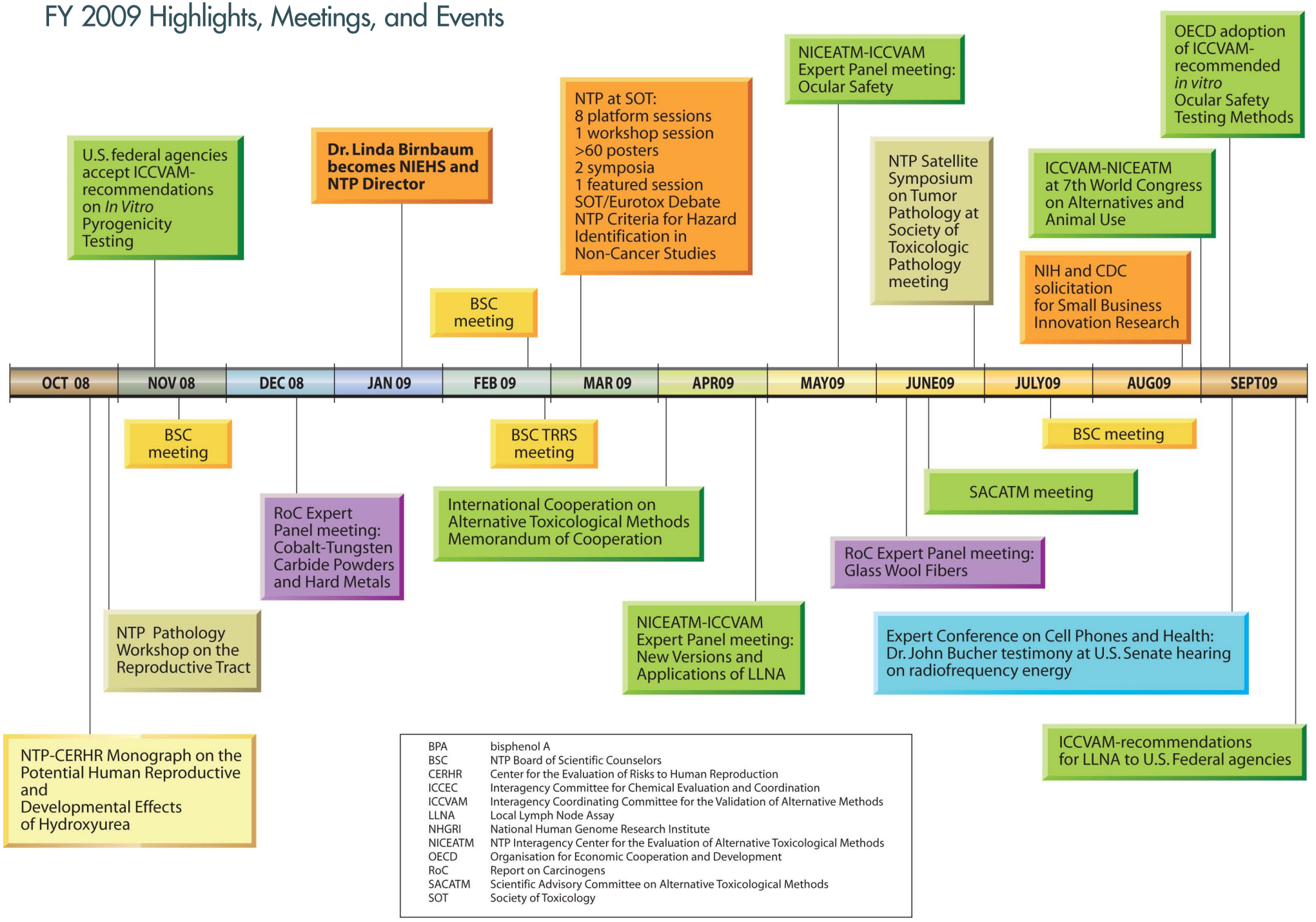
The NTP continues to be a leader in evaluating agents of public health concern with our assessment of the potential adverse health effects of radiation emitted by cellular phones and cell towers. Dr. John Bucher, NTP Associate Director, briefed the U.S. Senate on radiofrequency energy and NTP participated in the *Expert Conference on Cell Phones and Health: Science and Public Policy Questions*. Another important effort is the study of fullerenes, carbon nanotubes, and nanoscale metals and NTP has published *A 21st Century Paradigm for Evaluating the Health Hazards of Nanoscale Materials*. We have completed an evaluation of the potential human reproductive and developmental effects of hydroxyurea and are evaluating soy infant formula for developmental effects. We conducted a Workshop on the Reproductive Tract and played a lead role in establishing *International Harmonization of Nomenclature and Diagnostic Criteria* for non-neoplastic lesions. We concluded the scientific review of eight candidate substances under consideration for the 12th Report on Carcinogens and completed our first two Technical Reports on dietary supplements, androstenedione and goldenseal root powder.

The NTP Criteria for Hazard Identification in Non-cancer Studies were unveiled at the 2009 Society of Toxicology (SOT) meeting. Also at SOT, we had an array of platform sessions, symposia, workshops, and posters, to disseminate our findings on the health effects of exposures to chemical mixtures, DNA-based therapies, dietary supplements, phototoxicants, occupationally relevant substances, and mold. Using state-of-the-science bioinformatics, computational toxicology, alternative toxicological methods, and disposition/pharmacokinetics, NTP continues to work with our agency partners and our scientific advisory boards to stay at the cutting edge of scientific research.

Linda Birnbaum

Linda S. Birnbaum, PhD, DABT, ATS

FY 2009 Highlights, Meetings, and Events



BPA	bisphenol A
BSC	NTP Board of Scientific Counselors
CERHR	Center for the Evaluation of Risks to Human Reproduction
ICCEC	Interagency Committee for Chemical Evaluation and Coordination
ICCVAM	Interagency Coordinating Committee for the Validation of Alternative Methods
LLNA	Local Lymph Node Assay
NHGRI	National Human Genome Research Institute
NICEATM	NTP Interagency Center for the Evaluation of Alternative Toxicological Methods
OECD	Organisation for Economic Cooperation and Development
RoC	Report on Carcinogens
SACATM	Scientific Advisory Committee on Alternative Toxicological Methods
SOT	Society of Toxicology

Overview of the National Toxicology Program

Mission and Goals

Currently, the Toxic Substances Control Act Chemical Substance Inventory *(http://www.epa.gov/oppt/newchems/pubs/invntory.htm)*, first published in 1979, lists more than 80,000 chemicals as being available for sale and use in the United States. Approximately 850 active pesticide ingredients are formulated into approximately 17,000 pesticide products. An estimated 500 to 600 new industrial chemicals are introduced annually into U.S. commerce. The effects of many of these substances on human health are unknown, yet people and our environment may be exposed to them during their manufacture, distribution, use, and disposal or as pollutants in our air, water, or soil. While relatively few substances are thought to pose a significant risk to human health, safeguarding the public depends upon identifying the effects of these agents, and of certain naturally occurring chemicals, and determining the levels of exposure at which they may become potentially hazardous to humans.

NTP MISSION:

TO EVALUATE AGENTS OF PUBLIC HEALTH CONCERN BY DEVELOPING AND APPLYING THE TOOLS OF MODERN TOXICOLOGY AND MOLECULAR BIOLOGY

The Department of Health Education and Welfare (now the Department of Health and Human Services, DHHS) established the National Toxicology Program (NTP) in 1978 as a focal point to coordinate toxicology testing in the federal government. In carrying out its mission, the NTP has several goals to:

- provide evaluations of substances of public health concern
- develop and validate improved (sensitive, specific, rapid) testing methods
- develop approaches and generate data to strengthen the science base for risk assessment
- communicate with all stakeholders including government, industry, academia, the environmental community, and the public

Organizational Structure and Oversight

Three agencies, the National Institute of Environmental Health Sciences (NIEHS) of the National Institutes of Health, the National Institute for Occupational Safety and Health (NIOSH) of the Centers for Disease Control and Prevention, and the National Center for Toxicological Research (NCTR) of the Food and Drug Administration, form the core for the NTP (Figure 1). The NTP is located at the NIEHS, and the Director of the NIEHS serves as the NTP Director. Questions and inquiries about the NTP can be directed to the NTP Office of Liaison, Policy and Review (919-541-7539) or *CDM@niehs.nih.gov*.

NTP Management during FY 2009

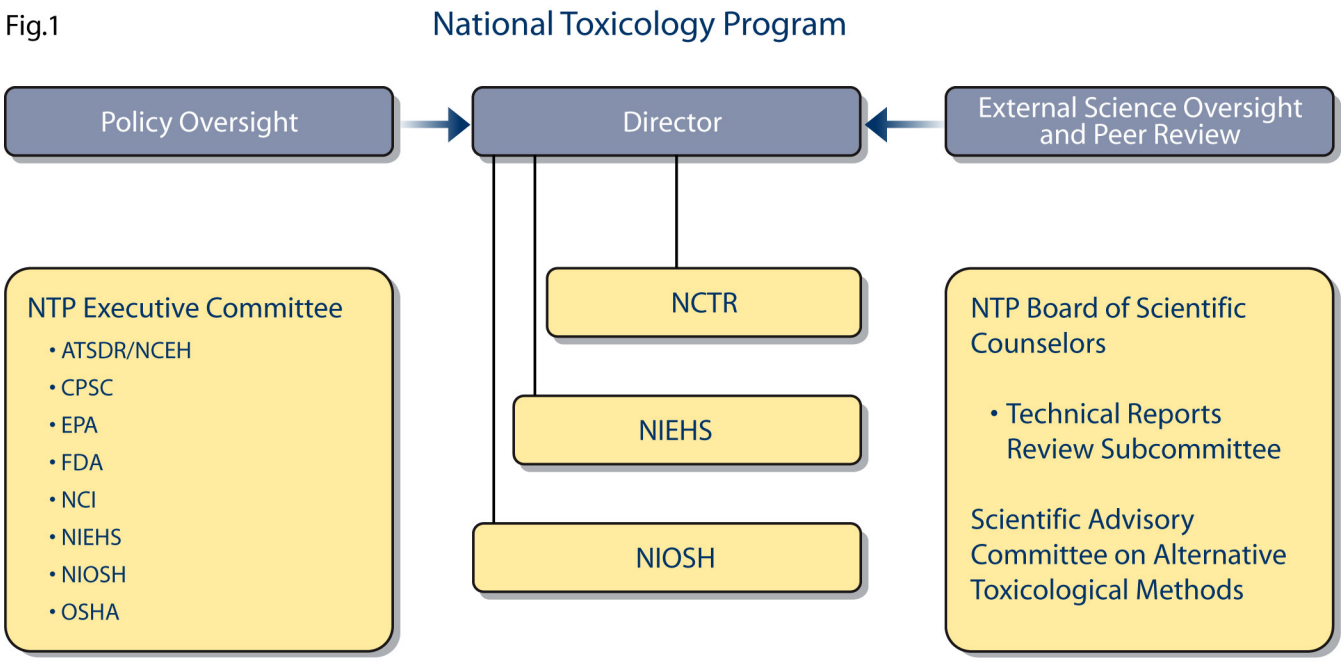
Dr. Samuel Wilson, Acting Director of NIEHS and NTP (until January 2009)
Dr. Linda Birnbaum, Director of NIEHS and NTP (starting January 2009)

Agency Program Management

NCTR: Dr. Paul Howard, Associate Director, Office of Scientific Coordination
NIEHS: Dr. John Bucher, Associate Director, NTP
NIOSH: Dr. Mark Toraason, Senior Fellow, Division of Applied Research and Technology

Staff of the agencies involved with the program and their contact information are provided in Appendix 1.

Fig.1



Addressing Scientific, Regulatory, and Public Needs

The NTP is flexible and innovative in its approach toward addressing public health concerns related to exposures to chemical and physical agents at home, in the workplace, and in the environment. Over the years since its inception to take over the National Cancer Institute's (NCI's) cancer bioassy program, the NTP has expanded its scope beyond cancer to include examining the impact of substances on non-cancer outcomes, such as those affecting reproduction and development and the immune, respiratory, nervous, cardiovascular, and endocrine systems.

The NTP recognizes that initiatives addressing critical gaps in knowledge needed to evaluate environmental toxicants offer the best opportunities for preventing environmentally mediated diseases. Therefore, the NTP's testing of substances continues to evolve to include more mechanism-based toxicology studies that focus on understanding the modes of action of agents under study. In recent years, the NTP has placed a greater emphasis on providing human relevance in interpreting and understanding toxicological information created from animal

or *in vitro* cell models. This is important if we are to be at the forefront in research efforts to improve methods to assess risk that account for the entire sequence of events from initial chemical exposure to ultimate toxicity. Examples of activities the NTP covers include:

- Increased use of both information on mechanisms of action and scientific judgment in deliberations for listings in the Report on Carcinogens
- Increased efforts to examine alternative testing methods that may provide better information than current models while using fewer animals or causing less pain or distress, and may provide better data for risk assessments
- Increased efforts to collect information on (1) a broader variety of both environmental and occupational exposures, (2) potentially toxic mixtures of compounds, and (3) susceptibilities based on life stages (e.g., neonatal, elderly)

Internationally, the NTP rodent bioassay is recognized as the standard for identifying carcinogenic agents; however, the NTP continues to work to reduce, refine, and replace the use of experimental animals and to develop and validate alternative testing methods. This effort led to the creation of the NTP Interagency Center for the Evaluation of Alternative Toxicological Methods (NICEATM) in 1998. The NTP will continue to work with the Interagency Coordinating Committee for the Validation of Alternative Methods (ICCVAM) through NICEATM in promoting the development, validation, and regulatory acceptance of new and revised alternative toxicological methods.

Strengthening existing partnerships and forging new ones are important to achieve NTP goals. Partnerships with other sister Federal agencies are increasing (interagency agreements [IAGs] are presented on page 77). The NTP continues to support an effort to evaluate the phototoxicity of various compounds through the NTP Center for Phototoxicology at the NCTR. The NTP is also contributing to toxicological assessments of emerging issues, such as nanotechnology, radiofrequency radiation emissions from cellular phones, herbal medicines/dietary supplements, water disinfection by-products, and phthalates, and will provide this information to other agencies.

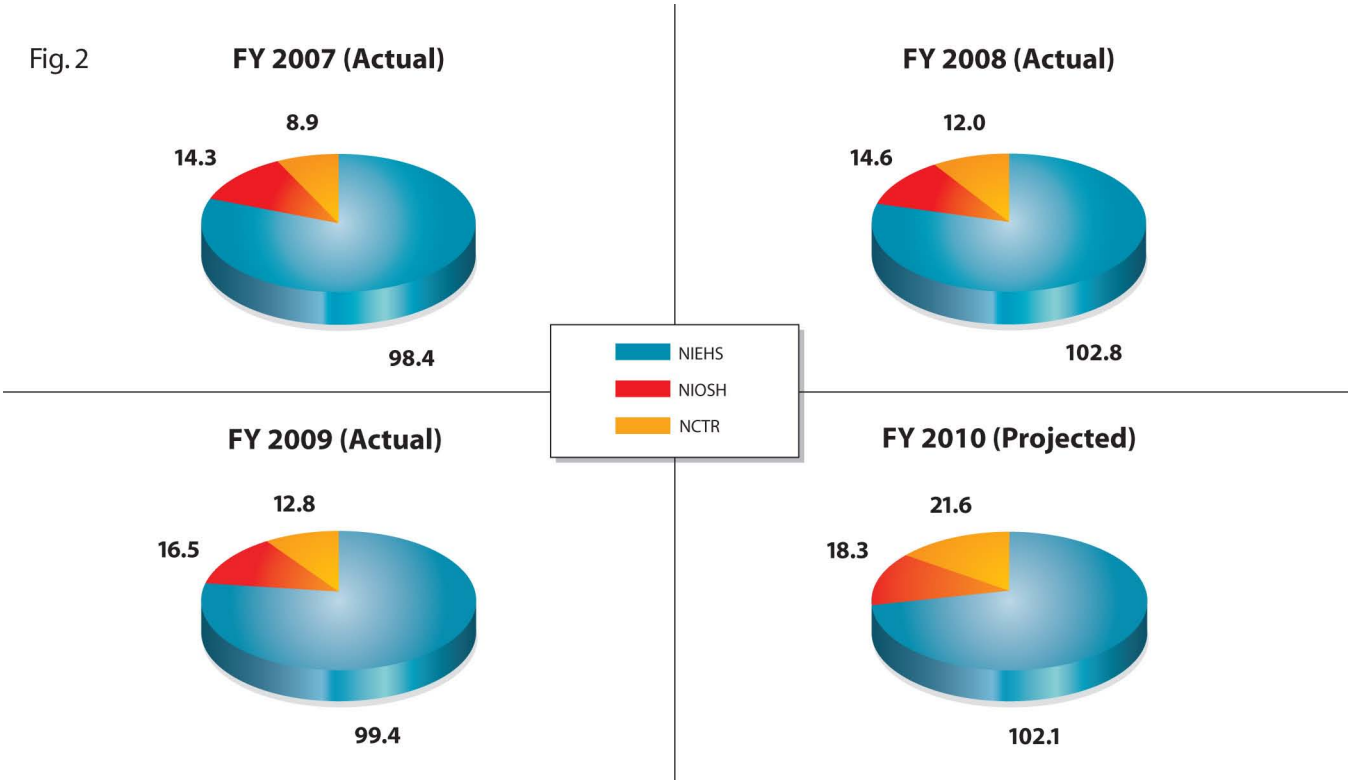
Regulatory agencies make decisions to protect public health based on scientific information from several sources (e.g., toxicology, human studies, and basic research). The NTP plays a critical role in providing needed scientific data, interpretation, and guidance in the appropriate uses of these data, to regulatory agencies as well as other groups involved in health-related research. The NTP is committed to using the best science available in setting priorities for future studies and in designing, conducting, and interpreting the findings of those studies. The American people and government agencies at state and Federal levels rely on the NTP to provide a strong scientific basis for making credible decisions that will protect public health. The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and is recognized by many groups for its scientific rigor, objectivity, and open approach in the continuing dialogue on appropriately applying scientific advances to applied toxicology research and testing.

Resources and Planning

Current and Projected Research Capacity

The NTP relies on voluntary allocations from the program's three core agencies (NIEHS, NCTR, and NIOSH) to support its various programs and initiatives. These allocations are specified after yearly appropriations are determined. As shown in Figure 2, the actual total allocations from the principals toward the NTP have dropped slightly from FY 2008 to FY 2009. For FY 2010 there is a projected 10% increase in funding. The NTP conducts its research studies mainly through contract laboratories or in-house at the core agencies, but also supports IAGs with other Federal agencies. Funds are used to sponsor workshops and conferences and to produce and distribute printed programmatic materials. In FY 2009, the NIEHS funded 35 contracts and held two peer-review and two expert-panel meetings for the NTP. The NIEHS also funded IAGs with NIOSH, NCTR, EPA, and the NIH Chemical Genomics Center and held four scientific advisory meetings.

Fig. 2



The NTP maintains an objective, science-based approach in dealing with critical issues in toxicology and continually sets priorities to improve the nation's ability to evaluate the human health effects caused by environmental exposures.

In summary, the NTP is a comprehensive research program spanning several agencies committed to providing resources to support the NTP's research and to communicating the knowledge learned to all stakeholders, public and private. The NTP's efforts in testing, research, and assessing health hazards work to obtain the best scientifically valid data for health regulatory and research agencies to use to make appropriate decisions about potential human risks from exposure to environmental toxicants. Toward that end, the NTP is continually evolving to remain at the cutting edge of scientific research and development and application of technology.

Advisory Boards and Committees

As shown in Figure 1, the NTP relys on a number of external boards and committees for science and policy oversight and peer review. As needed, the program convenes Special Emphasis Panels and Working Groups to address specific topics.

NTP Board of Scientific Counselors

The NTP Board of Scientific Counselors (BSC), a Federally chartered advisory group, provides scientific oversight to the NTP, including the Report on Carcinogens (RoC) Center and the Center for Evaluation of Risks to Human Reproduction (CERHR). The Secretary of DHHS appoints members to the BSC. The BSC can consist of up to 35 scientists, primarily from the public and private sectors, with scientific expertise relevant to the NTP's activities. The BSC members serve rotating terms of up to four years and the BSC typically meets twice per year. Opportunities for public comment are scheduled at all meetings. The BSC's Technical Reports Review Subcommittee (TRRS) generally meets once a year and provides peer review of draft NTP long-term toxicology and carcinogenesis technical reports. The NTP Executive Secretary, Dr. Barbara Shane, managed the BSC in FY 2009. A list of members during FY 2009 is provided in Table 1.

BSC meetings in FY 2009

The BSC met on November 20-21, 2008, at the NIEHS in Research Triangle Park, NC. The BSC reviewers:

- Provided input on proposed NTP study concepts for five nominations to the testing program (dimethylamine borane, ethylene glycol 2-ethylhexyl ether, bisphenol AF, β-*N*-methylamino-L-alanine, and triclosan)
- Accepted a report from working groups convened to address levels of evidence criteria for evaluating outcomes for NTP immunotoxicology studies, NTP reproductive toxicology studies, and NTP developmental toxicology studies
- Reviewed a contract concept to procure mold materials for planned NTP studies
- Heard overviews of NTP studies on DNA-based therapies and toxicogenomics, including the use of toxicogenomics to predict the potential of alkoxypropenylbenzenes to cause liver cancer
- Provided input on the High Throughput Screening (HTS) Initiative

A second FY 2009 BSC meeting was held on February 24, 2009, at the NIEHS. Dr. Linda Birnbaum, Director of NIEHS and NTP, outlined her visions for the NIEHS and NTP. The remainder of the meeting was devoted to peer review relating to the 12th RoC. The BSC, supplemented with ad hoc scientific experts, peer-reviewed draft substance profiles for five candidate substances for the 12th RoC (aristolochic acids, captafol, *ortho*-nitrotoluene, riddelliine, and styrene). The BSC heard background information on the RoC and the process for its preparation and supported the NTP's preliminary policy decisions regarding the listing status of the five candidate substances.

The BSC met again on July 23-24, 2009, at the NIEHS. Dr. Birnbaum reported on activities at the NIEHS and NTP since the February BSC meeting. The chair of the BSC TRRS presented the subcommittee's recommendations on the findings and conclusions of six draft NTP Technical Reports on conventional rodents that were peer-reviewed at a meeting on February 25, 2009. The BSC:

- Unanimously accepted the subcommittee's recommendations for the draft reports
- Provided input to the NTP on proposed study concepts for six nominations to the testing program (alkylanilines, deoxynivalenol, dong quai, indium tin oxide, *p*-chlorobenzotrifluoride, tris(4-chlorophenyl) methane, and tris(4-chlorophenyl)methanol)

- Reviewed and approved three concepts for contracts to provide research support for (1) NTP toxicology and carcinogenicity studies, (2) preparation of the RoC, and (3) investigative absorption, distribution, metabolism, and excretion (ADME) studies of toxicants in NTP animal model systems
- Heard presentations on studies supported through NIEHS/NTP IAGs with the NCTR and NIOSH

Additional information about the BSC, including minutes from its meetings, is available on the NTP website *http://ntp.niehs.nih.gov/go/164* or from Dr. Lori White, BSC Designated Federal Officer (*whiteld@niehs.nih.gov*).

TRRS meetings in FY 2009

The NTP BSC TRRS met in public forum on February 25, 2009, at the NIEHS. The subcommittee peer reviewed the findings and conclusions of six draft NTP Technical Reports (androstenedione, goldenseal root powder, β-myrcene, 2,3′,4,4′,5-pentachlorobiphenyl, 3,3′,4,4′-tetrachloroazobenzene, and tetralin) of studies that used conventional rodent models. The subcommittee's recommendations were reported to the BSC at the July 23-24, 2009, meeting.

Table 1. NTP Board of Scientific Counselors Membership Roster FY 2009

Name and Title	Affiliation	Term Ends	BSC Service
Tracie E. Bunton, DVM, PhD, DACVP Toxicology Consultant	Eicarte LLC Fairfield, PA	6/30/10	BSC and TRRS
Edward W. Carney, PhD Technical Leader, Developmental, Reproductive and General Toxicology	The Dow Chemical Company Midland, MI	6/30/10	BSC
Russell C. Cattley, VMD, PhD Executive Director Pathology	Amgen Thousand Oaks, CA	06/30/10	BSC and TRRS
David A. Eastmond, PhD Professor and Chair, Department of Cell Biology and Neuroscience	University of California Riverside, CA	06/30/12	BSC and TRRS
Elaine M. Faustman, PhD Professor and Director, Institute for Risk Analysis and Risk Communication; Department of Environmental and Occupational Health Sciences	University of Washington Seattle, WA	06/30/12	BSC
Kenny S. Crump, PhD Research Professor	Louisiana Tech University Ruston, LA	12/27/08	BSC and TRRS
George Friedman-Jiménez, MD Assistant Professor, Departments of Environmental Medicine and Medicine	New York University School of Medicine New York, NY	12/27/09	BSC
S. Katherine Hammond, PhD, CIH Professor of Public Health	University of California Berkeley, CA	12/27/08	BSC
William P. Janzen Professor, Division of Medicinal Chemistry and Natural Products; Director, Assay Development and Compound Profiling	University of North Carolina at Chapel Hill, NC	06/30/10	BSC
Nancy I. Kerkvliet, PhD Professor, Immunotoxicology and Extension Toxicologist Specialist	Oregon State University Corvallis, OR	12/27/08	BSC and TRRS
Stephen W. Looney, PhD Professor, Department of Biostatistics, Department of Oral Health and Diagnostic Science	Medical College of Georgia Augusta, GA	06/30/12	BSC and TRRS
D. Gail McCarver, MD (chair through 12/08) Co-Director, Department of Pediatrics	Medical College of Wisconsin Milwaukee, WI	12/27/08	BSC

Name and Title	Affiliation	Term Ends	BSC Service
Jon C. Mirsalis, PhD Managing Director, Biosciences Division	SRI International Menlo Park, CA	12/27/08	BSC and TRRS
Mitzi Nagarkatti, PhD Professor and Chair, Department of Pathology, Microbiology and Immunology	University of South Carolina School of Medicine Columbia, SC	06/30/11	BSC and TRRS
Raymond F. Novak, PhD Director, Institute of Environmental Health Sciences	Wayne State University Detroit, MI	06/30/10	BSC and TRRS
Michael V. Pino, DVM, PhD Director of Pathology	Sanofi-Aventis Bridgewater, NJ	12/27/09	BSC and TRRS
Kenneth M. Portier, PhD (chair 1/09 – 12/09) Director of Statistics	American Cancer Society Atlanta, GA	12/27/09	BSC and TRRS
Jim E. Riviere, DVM, PhD, ATS Burroughs Wellcome Fund Distinguished Professor of Pharmacology	North Carolina State University Raleigh, NC	12/27/09	BSC and TRRS
Diane M. Robins, PhD Professor, Department of Human Genetics	University of Michigan Medical School Ann Arbor, MI	12/27/09	BSC
Ruthann A. Rudel, MS Senior Scientist, Toxicology and Environmental Health Risk Assessment	Silent Spring Institute Newton, MA	06/30/11	BSC
James L. Sherley, MD, PhD Senior Scientist	Boston Biomedical Research Institute Watertown, MA	06/30/11	BSC and TRRS
Gina M. Solomon, MD, MPH Senior Scientist	Natural Resources Defense Council San Francisco, CA	06/30/11	BSC
Keith A. Soper, PhD Senior Director, Biometrics Research	Merck West Point, PA	12/27/08	BSC and TRR
Justin G. Teeguarden, PhD Senior Scientist, Fundamental and Computational Sciences Directorate	Pacific Northwest National Laboratory Richland, WA	06/30/11	BSC and TRR
David H. Wegman, MD, MSc Dean	University of Massachusetts Lowell, MA	06/30/09	BSC

Scientific Advisory Committee on Alternative Toxicological Methods

The Scientific Advisory Committee on Alternative Toxicological Methods (SACATM) is a federally chartered advisory committee established on January 9, 2002, in response to the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3(d)). SACATM advises ICCVAM, NICEATM, and the Director of the NIEHS regarding statutorily mandated duties of ICCVAM and activities of NICEATM (see page 37). SACATM provides advice on priorities and activities related to the development, validation, scientific review, regulatory acceptance, implementation, and national and international harmonization of new, revised, and alternative toxicological test methods. Alternative methods are those that reduce, refine (lessen or avoid pain and/or distress), or replace the use of animals in testing. SACATM also provides input on ways to foster partnerships and communication with interested parties. The NIEHS Director appoints 15 voting members to the SACATM, and membership includes representatives drawn from academia, state government, industry, and animal protection organizations (Table 2). Members serve rotating terms of up to four years. SACATM typically meets once a year. The NTP Designated Federal Officer Dr. Lori White manages SACATM.

SACATM met on June 25 – 26, 2009, at the Hilton Arlington in Arlington, Virginia. SACATM was presented an overview of the National Research Council Report *Recognition and Alleviation of Pain in Laboratory Animals* and the NICEATM-ICCVAM Implementation Plan for 2008-2012. Two Federal agencies, EPA and the U.S. Department of Agriculture, provided updates of their research, development, translation, and validation activities relevant

to the NICEATM-ICCVAM Five-Year Plan. SACATM members supported the findings presented for two reports: (1) Report on the Independent Scientific Peer Review Panel on Alternative Ocular Safety Testing Methods and (2) Report on the Second Meeting of the Independent Peer Review Panel: Evaluation of the Updated Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay. SACATM was provided updates on NICEATM-ICCVAM activities and on the regulatory acceptance and availability of ICCVAM-recommended alternative test methods. SACATM members suggested ways to gain broader use of recommended methods. Liaisons from the European Centre for the Validation of Alternative Methods (ECVAM) and the Japanese Center for the Validation of Alternative Methods (JaCVAM) presented updates on the activities of their groups.

Table 2. Scientific Advisory Committee on Alternative Toxicological Methods Roster FY 2009

Name and Title	Affiliation	Term Ends
Frank Barile, PhD Associate Professor	St. John's University Jamaica, NY	06/30/09
Karen K. Brown, PhD President	Pair O' Docs Enterprises Parkville, MO	06/30/11
Marilyn J. Brown, DVM Executive Director, Animal Welfare and Training	Charles River Laboratories East Thetford, VT	06/30/09
Grantley D. Charles, PhD Senior Scientist, Toxicology	Allergan Irvine, CA	06/30/09
George B. Corcoran, PhD, ATS Professor and Chairman Department of Pharmaceutical Sciences	Wayne State University Detroit, MI	6/30/11
Helen E. Diggs, DVM, DACLAM Associate Dean, Hospital Program Director Veterinary Teaching Hospital	College of Veterinary Medicine, Oregon State University Corvallis, OR	06/30/10
Marion F. Ehrich, PhD Professor, Biomedical Sciences and Pathology/Laboratory for Neurotoxicity Studies	VA-MD Regional College of Veterinary Medicine Blacksburg, VA	06/30/10
Donald A. Fox, PhD Professor, Pharmacological and Pharmaceutical Sciences	University of Houston Houston, TX	06/30/09
James Freeman, PhD (chair) Distinguished Toxicology Associate	ExxonMobil Biomedical Sciences, Inc. Annandale, NJ	06/30/10
Steven R. Hansen, DVM, MS, MBA, DABT, ABVT Senior Vice President, Animal Health Services	ASPCA Animal Poison Control Center Urbana, IL	6/30/12
Daniel S. Marsman, DVM, PhD Section Head, Animal Welfare and Alternatives	Procter and Gamble Cincinnati, OH	06/30/09
Annie (Peiyong) Qu, PhD Associate Professor, Department of Statistics	University of Illinois at Urbana-Champaign Champaign, IL	06/30/10
Gary Wnorowski, MBA, LAT President	Eurofins/Product Safety Laboratories Dayton, NJ	6/30/11

Additional information about SACATM, including minutes from its meetings, is available on the NTP website *http://ntp.niehs.nih.gov/* (select "Advisory Board and Committees") or from Dr. Lori White, Designated Federal Officer, NIEHS *(whiteld@niehs.nih.gov)*.

NTP Executive Committee

The NTP Executive Committee provides programmatic and policy oversight to the NTP Director. The Executive Committee meets once or twice a year in closed forum. Members of this committee include the heads (or their designees) of the following Federal agencies:

- Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- Consumer Product Safety Commission
- Environmental Protection Agency
- Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

Interagency Committee for Chemical Evaluation and Coordination (ICCEC)

The Interagency Committee for Chemical Evaluation and Coordination (ICCEC) evaluates nominations to the NTP testing program and makes recommendations regarding specific types of toxicological studies and testing priorities. The ICCEC meets once or twice annually and consists of representatives from:

- Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- Consumer Product Safety Commission
- Department of Defense
- Environmental Protection Agency
- National Center for Toxicological Research
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institute for Occupational Safety and Health
- Occupational Safety and Health Administration

Interagency Coordinating Committee on the Validation of Alternative Methods (ICCVAM)

ICCVAM is a permanent interagency committee of the NIEHS under NICEATM. The committee was formally established in law by the ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3). The purpose of ICCVAM is to establish, wherever feasible, guidelines, recommendations, and regulations that promote the regulatory acceptance of new or revised scientifically valid toxicological tests that protect human and animal health and the environment while reducing, refining, or replacing animal tests and ensuring human safety and product effectiveness (see *http://iccvam.niehs.nih.gov/about/process.htm*). Dr. Marilyn Wind, CPSC, served as chair of ICCVAM in FY 2009. ICCVAM meets several times per year and consists of representatives from 15 Federal agencies that generate or use toxicological data to carry out their responsibilities to protect and improve the health and safety of people, animals, and the environment:

- Agency for Toxic Substances and Disease Registry/National Center for Environmental Health
- Consumer Product Safety Commission
- Department of Defense
- US Department of Agriculture
- Department of Energy
- Department of the Interior
- Department of Transportation
- Environmental Protection Agency
- Food and Drug Administration
- National Cancer Institute
- National Institute of Environmental Health Sciences
- National Institutes of Health
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NIOSH/NTP

NIOSH/NTP: Division of Applied Research and Technology

NIOSH/NTP: Division of Surveillance, Hazard Evaluations, and Field Studies

NIOSH/NTP: Health Effects Laboratory Division

The National Institute for Occupational Safety and Health (NIOSH) is the Federal agency responsible for conducting research and making recommendations for the prevention of work-related injury and illness. The mission of NIOSH is to generate new knowledge in the field of occupational safety and health and to transfer that knowledge into practice for the betterment of workers. To accomplish this mission, NIOSH conducts scientific research, develops guidance and authoritative recommendations, distributes information, and responds to requests for workplace Health Hazard Evaluations (HHEs).

NIOSH's participation in the NTP is consistent with its mandate to protect workers' health and safety under the Occupational Safety and Health Act and the Federal Mine Safety and Health Act. Setting priorities in occupational toxicological research is based upon several sources of information that are developed and maintained by NIOSH, including HHEs, industry-wide studies, gaps in knowledge identified while developing criteria for recommended standards or Criteria Documents, Current Intelligence Bulletins, hazard reviews or alerts, and other technical reports, and information profiles on chemical hazards. Toxicological research on important occupational chemicals is conducted in cellular and genetic toxicology, carcinogenesis research and testing, toxicological characterization, chemical disposition, neurobehavioral toxicology, reproductive and developmental toxicology, dermal toxicology, and exposure assessment. NIOSH research projects are conducted by the:

- Division of Applied Research and Technology – Cincinnati, Ohio
- Division of Surveillance, Hazard Evaluations, and Field Studies – Cincinnati, Ohio
- Health Effects Laboratory Division – Morgantown, West Virginia

NIOSH/NTP studies funded by NIOSH voluntary contributions are listed in Table 3.

Table 3: NIOSH/NTP Projects FY 2009*	
NIOSH/NTP [Project Officer]	**Objective and/or Project Summary**
Biomarker Development for Field Studies [B'Hymer]	To provide the biomonitoring analyses required for field investigations of occupational exposures. Biomarker methods will be developed and applied for occupational toxicants and applied to assess exposure and susceptibility. Efforts continued to the study on biomarkers of susceptibility, as they related to metabolism and DNA repair pathways, with respect to acrylamide and manicurists. These biomarker methods will improve the assessment of internal dose and early biological effects in field studies of occupational exposures.
Reproductive Health Assessment of Male Workers [Schrader]	To assess reproductive health hazards using a health profile consisting of biomarkers for evaluating male fecundity. Work focused on completing the Longitudinal Investigation of Fertility and the Environment (LIFE) project, a collaborative effort between NIOSH and the NIH National Institute of Child Health and Human Development. Data collected from bicycling police officers in the public and private service sector will be analyzed. A follow-up study of long-term use (1-3 years) of no-nose saddles will be conducted. This work includes development of new biomarkers to include in the male reproductive health profile.
Statistical Research Development and Planning [Krieg]	To provide statistical planning and analysis for all research done within the Division of Applied Research and Technology. This includes making power calculations, developing study designs, analyzing statistical data, and creating graphs and written reports that summarize the analyses and their results.
Immunochemical Biological Monitoring for Occupational Exposure and Disease [Striley]	To evaluate industrial and agricultural chemicals with known acute and chronic toxicities that present a significant exposure risk for workers. Biological monitoring can assess exposure by analyzing acute and latent metabolites in various biological media. The goal of this project is to develop low-cost, rapid biomonitoring methods using immunochemistry and analytical chemistry to identify exposures and evaluate potential interventions. This project will also identify and develop new multiplex immunochemical methods to evaluate biomarkers of occupational illness or subclinical signs of occupational illness.
Research Development and Planning [DeBord]	To provide scientific and administrative oversight for the Biomonitoring and Health Assessment Branch investigative research, methods development and collaborations in biological monitoring and biomarkers, reproductive health assessments, genotoxicity, genetics, immunochemistry, and immunotoxicology. The scientific management provided ensures that research activities are relevant to NIOSH goals, timely, and scientifically and fiscally sound. Results include biomarkers of exposure, effects of exposure, susceptibility to exposure, new research methods, reproductive health assessments, and journal publications, which are shared with internal and external partners.
Development of Urinary Metabolite Methods for Biomonitoring [B'Hymer]	To develop and validate test methods for quantification of urinary metabolites that can be used as biomarkers of exposure for hazardous workplace chemicals. The goal is to analyze archived specimens from current and past NIOSH studies. Research activities will be expanded later as new collaborative studies are developed. Results will include validated methods and various publications and/or presentations.
Assessing the Reproductive Health of Female Workers [Kesner]	To develop and apply methods to assess reproductive health of women exposed to occupational hazards, help with interventions to lessen hazardous impacts, and collaborate globally towards maximizing of these goals. Methods development focuses on specific, sensitive measures of female reproductive hormones and other biological markers of reproductive status in readily collectible body fluids, such as urine and saliva. Initial studies assess the effects of pesticides, polyhalogenated biphenyls, and metals on women's reproductive health in the agriculture, manufacturing, and mining sectors.
Biomonitoring Collaborative Research Studies [Lynch]	(1) To develop collaborative research for biological monitoring to support NIOSH's biological monitoring needs, including HHEs; (2) to coordinate NTP activities for NIOSH, which include participating in NTP committees and nominating chemicals of interest to the NTP for testing; and (3) to evaluate the role of genetic polymorphisms in influencing occupational diseases in collaboration with the CDC Genetics Working Group and the Brain Cancer Consortium.

**Funded by NIOSH voluntary allocations*

NIOSH/NTP [Project Officer]	Objective and Project Summary
Orthophthalaldehyde (OPA) Hazard Assessment [Toraason]	To assess occupational exposures to OPA, determine if these exposures cause adverse effects in health care workers, develop analytical methods for environmental monitoring of OPA, and determine the feasibility of an OPA biomarker. Because of the absence of published toxicological data on OPA, testing will be conducted in experimental animals and will focus on dermal and respiratory irritation and sensitization. Dose-response data will be obtained for risk assessment based on hazard identification, which along with health assessments will serve as the basis for establishing exposure limits.
Acrylamide Workers' Reproductive and Neurological Health [Moorman]	To determine exposures and potential reproductive and neurobehavioral effects in acrylamide-exposed workers in the manufacturing sector. Sampling and analysis of ambient and personal air levels has been completed, as well as hemoglobin adducts as internal dose markers at a major production facility. The project is also evaluating male workers with and without exposures to acrylamide for reproductive and neurological endpoints. Exposures are assessed by area and personal sampling, dermal sampling, reported exposure data, and exposure biomarkers.
Manicurists Exposure, Health Exposure Interventions [Reutman]	To investigate occupational exposures to manicurists, potential health effects, and possible interventions to decrease exposures. Partnerships with nail technician school programs are being developed to research optimal ventilation and workplace risk reduction practices, and to collect pilot data on ambient mixture exposure levels, biomarkers of internal dose, and health measures to preliminarily characterize the exposures and health of nail technicians. Expected outputs include: (1) feedback provided to manufacturers of a vented table that NIOSH evaluated for ventilation efficiency, potential ways to enhance it (if indicated), and other table features important for nail salon settings; (2) pilot data collected and analyzed to help design potential future intervention studies in nail salons; and (3) educational materials on workplace exposure and risk reduction developed based on these studies, with distribution to nail technician audiences.
Operating Room Personal Exposure to Chemotherapy Drugs [Connor]	To reduce occupational exposure to antineoplastic (AN) drugs in operating rooms during procedures on cancer patients. NIOSH will identify potential drug exposures by measuring drugs on work surfaces, in air samples, and in the urine of personnel. If exposures are identified, recommendations will be made for changes in work practices or types of safety equipment to help protect workers. The workplace will be re-evaluated after these interventions and findings will be reported to stakeholders.
Direct Reading Monitors for AN Drug Detection [Smith]	To prevent exposure of health care workers to AN drugs by developing portable instruments to measure surface contamination. These near real-time, direct-reading monitors will be tested in the laboratory and used in the field by health care workers. Commercial partners will be found to manufacture and market the monitors to make the monitors widely available to health care workers.
Detection of DNA Damage in Workers Exposed to JP-8 Jet Fuel [Butler]	To characterize the genotoxic health hazards associated with occupational exposure to jet propulsion fuel-8 (JP-8) and its civilian equivalents. Genotoxic hazards will be evaluated using existing exposure data and biological specimens archived from a research study conducted with the U.S. Air Force in 2000. Expected outputs include new data on the genotoxicity of jet fuel in humans, which may result in the development of risk communication products, engineering controls, personal protective practices, and new occupational health policies resulting in reduced exposures and improved health for workers exposed to jet fuel.
Agriculture Health Study, Pesticide Exposure Among Farmer (AHS) Applicators and Their Families [Hines]	To conduct pesticide exposure assessment research among farmers who are participating in the AHS, a collaborative research effort by NCI, NIEHS, and EPA to investigate health risks among the farming population. The project will focus on characterizing the exposure of farmer applicators to selected pesticides (fungicides) and evaluating determinants of exposure. Epidemiologic evidence suggests that pesticide exposures may be related to increased cancer risks among farmers. Obtaining exposure measurements on the AHS cohort should improve exposure classification strategies within the AHS.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Environmental and Take-Home Pesticide Exposures – Farm Families [Curwin]	To evaluate pesticide exposures among workers and special populations exposed to pesticides, including farm children, farmers, and agricultural workers handling treated commodities. The health effects of low-level chronic exposures to pesticides are still largely unknown and the potential for agricultural workers, farmers, and farm children to be subjected to these exposures is considerable. The project will involve field studies to ascertain the extent to which these populations are exposed to pesticides. A combination of environmental and biological sampling will be employed. Questionnaires will be administered along with observations to determine practices and behaviors that may contribute to exposure. The results of the study will be used to make recommendations for reducing pesticide exposure among these populations.
Phthalates Exposure Screening and Cohort Identification [Hines]	To measure phthalate exposures among workers in a variety of industries to identify populations for possible epidemiologic reproductive health research. Information from this project will also be used in a NIOSH study of birth defects and parental exposures. Three phthalates, di(2-ethylhexyl) phthalate (DEHP), dibutyl phthalate (DBP), and diethyl phthalate, were selected for exposure monitoring based on toxicity, use, and National Health and Nutrition Examination Survey urine levels. Exposure information obtained in this project will be useful to groups interested in conducting human reproductive health studies on phthalates.
A Case-Control Study of Primary Intracranial Gliomas Among Rural Residents [Ruder]	To assess the increase in brain cancer and its etiology among farmers, an occupational group with excess risk for brain cancer. Using a case-control design, this study is evaluating associations between rural exposures and primary intracranial gliomas, the most common type of brain tumors, among male and female rural residents in four upper Midwestern states. It focuses on determining whether pesticides, *N*-nitroso compounds, electromagnetic fields, biological agents, and solvents are associated with increased glioma risk.
Flight Crew Studies [Grajewski]	To evaluate the health effects of work as a flight crew member. Workplace exposures that may potentially contribute to adverse health outcomes include cosmic ionizing radiation and alterations of circadian rhythm. Several studies are under way to examine the risk of adverse reproductive health outcomes, cancer, and mortality. These studies will provide useful health information to the 198,000 flight crew members, as well as frequent fliers, shift workers, and workers exposed to ionizing radiation.
Titanium Dioxide (TiO_2) Nanoparticle Exposure Study [Curwin]	To collect occupational exposure information for workers exposed to ultrafine and fine TiO_2. The data will be used by the Education and Information Division to provide information for the Current Intelligence Bulletin on TiO_2. The study objectives are (1) to develop a strategy to measure exposure to ultrafine particles, (2) to characterize exposure to ultrafine and fine TiO_2 for various jobs and tasks at various facilities manufacturing and using TiO_2, and (3) to evaluate a strategy for measuring workplace exposure to fine and ultrafine TiO_2.
Inhalation Facility Support [Chen]	To provide resources for the Health Effects Laboratory Division Inhalation Facility. Inhalation exposures are conducted to simulate and mimic workplace respiratory environmental conditions. The effects of inhalation exposures on laboratory animals are analyzed to investigate the causes and mechanism(s) of respiratory occupational diseases. The effects of gaseous and particulate toxicants are explored along with their dose-response and synergistic relationships.
Identification of Occupational Allergens [Beezhold]	To address concerns regarding exposures to substances that can cause inflammatory or immune reactions by developing improved techniques to detect these reactions before adverse clinical outcomes occur and by developing improved techniques to detect and identify inciting occupational agents. The project will involve the analyses of clinical samples, environmental bulk samples, and environmental aerosol samples.
Mineral Dust-induced Gene (MDIG) and Occupational Lung Diseases [Chen]	To understand how the MDIG is regulated upon exposure to inhaled particles and the role of MDIG in pulmonary disease. The hypothesis is that inducing MDIG is critically involved in silica-induced fibrosis and/or cancer. This project will use molecular biology techniques to define the transcriptional regulation and function of this novel gene. Results will improve understanding of mechanisms of pathogenesis and may help develop useful biomarkers for early detection or treatment of mineral dust-induced lung diseases in humans.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Systematic Microvascular Dysfunction Effects of Ultrafine Particles versus Fine Particles [Castranova]	To define the possible adverse health and environmental impact effects of exposure to nanomaterials and determine if pulmonary exposure to nanoparticles causes cardiovascular dysfunction. Data will be disseminated by presentation at scientific meetings, publications in journals, summaries in the NIOSH e-News and Nanotech Web page, and meetings with partners.
Evaluation of the Pulmonary Deposition and Translocation of Nanomaterials [Mercer]	To identify where in the lungs inhaled nanomaterials might deposit, the health risks that might arise from nanomaterial deposition, and to what extent they might translocate to other organs after depositing in the lungs. Results of this study will address critical issues identified by the NIOSH Nanotechnology Research Center and assist in hazard identification and risk assessment.
Dermal Effects of Nanoparticles [Shvedova]	To assess whether nanoparticles could cause adverse effects to skin. The hypothesis is that nanoparticles are toxic to the skin and that the toxicity depends on their penetration into skin, their induction of oxidative stress, and their content of transition metals. Results obtained provide critical knowledge about mechanisms of dermal toxicity of nanoscale materials and will be used by regulatory agencies (OSHA and EPA) and industry to address strategies to assure healthy work practices and safe environments.
Effect of Stainless Steel Welding Fume Particulate on Lung Immunity in Mice [Anderson]	To evaluate the effect of occupational exposure to manual metal arc stainless steel welding fumes on the immune system. Based on previous research and preliminary data, the hypothesis that exposure to chronic welding fumes suppresses the immune system by decreasing antibody production will be tested. If altered antibody production is confirmed, its potential mechanism of action will be determined by analyzing cellular populations and cytokine levels.
Development of New Immunodiagnostic and Detection Techniques for Indoor Fungi [Green]	To address problems associated with measuring personal exposure to *Paecilomyces variotii* fungus in occupational settings by identifying the major allergens and to produce species-specific monoclonal antibodies towards these allergens. These antibodies will then be used to create practical immunoassays to detect this fungus in clinical and environmental samples.
The Transient Dermal Exposure: Model and Experiments [Frasch]	To enhance knowledge and understanding of how industrial chemicals penetrate the skin after the types of exposure that occur in occupational settings. Data from *in vitro* skin penetration experiments will be compared with predictions of computer models to enhance their predictive value. A final product of this research will be a user-friendly, interactive, web-based calculator that can estimate the amount of chemical that penetrates the skin during workplace exposures.
Indoor Environment Nitrate Radical Chemistry [Ham]	To develop methods for sampling and analysis of indoor reaction products, and to use these methods to determine the potential for exposure in workplaces and homes.
Indoor Chemistry of Consumer Product Mixtures [Wells]	To investigate indoor reactant/consumer product reactions to more clearly define indoor workplace exposure, provide insight into important chemical structure(s) that influence indoor air quality, and highlight potential analytical/sampling needs. The research direction will be influenced by indoor environment research, such as indoor pollutant characterization and measurements. The research results will yield more accurate exposure assessments, better analytical tools for HHE sampling, and improved engineering control methods to reduce chemical contaminants.
Welding Fume Metals Exposure Matrix Determination [Keane]	To develop enhanced exposure assessment approaches for welding fumes by detailed speciation of manganese and chromium forms in the fumes and investigating biologically available metals in simulated biological fluids. This approach will be applied to a spectrum of welding processes including gas metal arc steel and stainless steel and manual arc stainless steel, as well as altered stainless steel processes using alternate shield gases of higher and lower oxygen content to estimate the effect on toxic entities such as hexavalent chromium and oxidized manganese species. Metal ion content in simulated plasma, lysosoma fluid, and simulated pulmonary surfactant will be measured. Outputs will include peer-reviewed publications, presentations, close collaboration with ongoing toxicology studies already in progress, and communications with welding equipment manufacturers.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Determination of Diameter Distribution for Carbon Nanotubes (CNTs) by Raman Spectroscopy [Chirila]	To use Raman spectroscopy for evaluating the diameter distribution of CNTs. By recording spectra using different laser lines, a broad diameter distribution can be determined. The process of dispersion of CNTs can be used to obtain and to measure isolated CNTs and to calculate a relative number of isolated versus bundled CNTs. The results from these studies will allow NIOSH to understand the possible state of agglomeration of the CNTs if they are inhaled and come in contact with pulmonary surfactant.
Dermal Penetration of Metal Working Fluid (MWF) Components [Frasch]	To obtain data on the permeation through skin of selected MWFs, using hairless guinea pig skin as a surrogate for human skin. MWF components will be selected for study based on known or suspected potential for adverse dermal effects, including irritant and allergic dermatitis and toxicity to the body. Dermal absorption rates will be compared between new, unused fluid and used fluid obtained from an industrial machining operation.
Particle Size Distributions and Lead Content in Aerosol Exposures from Metal Processing Facilities [Chisholm]	To contribute recommendations in sampling procedures to meet the International Standards Organization inhalable sampling conventions. The principal goal is to assess the value of the standard closed-face cassette total dust personal sampler as a biologically relevant sampler of lead-containing aerosols in typical occupational exposures. To achieve this goal, it is necessary to (1) develop a method to relate measurement of a particle's projected area in a scanning electron microscope image to its aerodynamic equivalent diameter, and (2) determine the masses and particle size distributions of the filter catches and wall deposits of closed-face cassette and Institute of Occupational Medicine samplers for both laboratory and field samples of lead-containing particles.
Neurotoxicity after Pulmonary Exposure to Welding Fumes containing Manganese [Antonini]	To assess the pulmonary and neurotoxic effects of animals exposed by inhalation to welding fumes that are composed of varying concentrations of manganese. Results will provide mechanistic information concerning welding fume exposure and be useful for risk assessment and the development of prevention strategies to protect exposed workers.
Pulmonary Toxicity of Metal Oxide Nanospheres and Nanowires [Porter]	To provide fundamental toxicological data on the exposure hazard posed by exposure to TiO_2 nanospheres and nanowires. Data obtained will (1) increase our understanding of how TiO_2 nanoparticle shape affects toxicological responses, (2) determine critical physico-chemical factors that could be exploited to reduce nanoparticle toxicity, and (3) provide a basis for initial hazard identification. These data could also contribute to risk assessment studies that may ultimately establish exposure standards and recommended handling practices to avert significant human health risks in the future.
Immune and Inflammatory Aspects of Occupational Rhinitis [Johnson]	To understand the mechanisms of occupational rhinitis in occupational safety, health, and medicine. A combined study design using human and animal research will be employed to identify the orthologously conserved pathways and gene networks that characterize the pathobiology of occupational rhinitis induced by diisocyanates. The outcomes of this research will benefit occupational safety and health through improved diagnosis and prevention of allergic airways disease caused by diisocyanates.
Genetics in Occupational Diseases [Yucesoy]	To use high-density and high throughput genotyping to investigate susceptibility gene variants that contribute to the development and severity of occupational irritant contact dermatitis and asthma. Previous and ongoing studies showed that cytokine polymorphisms have a major influence on silicosis, dementia, accelerated decline in lung function, and vaccine efficacy. Understanding genetic contributions to the development, progression, and outcomes of complex occupational diseases will help improve the accuracy of risk assessment and improve safe exposure levels for genetically susceptible groups in the workforce. This information could ultimately help identify novel therapeutic targets and preventive strategies for better management of work-related diseases.
Occupational Exposures and Potential Neurological Risks [Sriram]	To evaluate the adverse neurotoxicological effects of ultrafine and fine particles generated at the workplace. Occupational exposure to aerosolized ultrafine and fine particulates can result in translocation of these materials to the brain and elicit transient, irreversible, or progressive damage to the nervous system. A three-tier approach to evaluate neurotoxicity will be implemented. Results from this study will aid in development of biomonitoring protocols and hazard and risk assessment paradigms and will significantly contribute to occupational safety standards.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Cutaneous Bioactivation of Xenobiotics: Hapten versus Prohapten [Siegel]	To develop an *in vivo* model of allergic skin sensitization that can discriminate between chemicals requiring metabolic activation for sensitization (prohaptens) and those that can sensitize without biological activation (haptens). The model will involve the dermal application of various pharmacological inhibitors of the cytochrome P450 (CYP) pathway prior to performing either the local lymph node assay (LLNA) and/or mouse ear swelling test. Selective inhibition of the CYP pathway should distinguish between direct acting haptens and metabolically activated pro-haptens. Validation of the models will be done using known direct acting haptens and pro-haptens. Successful development of these models will produce data that strengthens *in silico* hazard predictive models and allows for substitution or modification of allergenic chemicals and drugs.
Lung Effects of Resistance Spot Welding Using Adhesives [Antonini]	To determine which component of aerosols generated during resistance spot welding may be potentially toxic to exposed workers. A robotic welding arm in the NIOSH welding lab will be configured and programmed to perform resistance spot welding to expose laboratory animals using process parameters common in the automotive industry. With the information collected from the proposed study, it may be possible to eliminate or substitute with more inert chemicals the components of the process that are most hazardous to a significant number of workers.
Potential Effects of Silicon-based Nanowires on Lung Toxicity [Leonard]	To investigate pulmonary toxicity associated with silicon nanowires. Cellular and cell-free systems will be used to determine the potential for nanowire samples to produce toxins. An animal model will be used to define the potential of the nanowires to induce lung injury, inflammation, oxidative stress, and disease *in vivo*. Information collected from the proposed study may be used to develop Material Safety Data Sheets, exposure limits, and safe workplace practices to reduce respiratory disease in the nanotechnology manufacturing sector.
Pathophysiology of Popcorn Workers' Lung [Hubbs]	To investigate the hypothesis that Popcorn Workers' Lung is an expression of the toxicity of flavoring vapors on the airway epithelium. Inhalation of microwave popcorn butter flavoring by food manufacturing workers causes Popcorn Workers' Lung, an emerging, life-threatening lung disease characterized by fixed airway obstruction. *In vivo* and *in vitro* animal models will investigate the dose-response relationship for individual flavorings and mixtures to identify hazards, define No Observable Effect Levels, and determine the pathophysiologic mechanism(s) for the airway epithelial toxicity of flavorings. This project will provide data for hazard identification, risk assessment, and recommended workplace exposure standards.
Respirable Silica Measurements with High-Flow-Rate Samplers [Wu]	To evaluate the application of high-flow-rate samplers compared with current low-flow-rate cyclone samplers. The performance evaluation results will assist the investigation of size distribution of silica-containing particles generated through mechanical processes, which will help determine potential effects of particle sizes in NIOSH particle studies.
Oxidative Mechanisms of Hexavalent Chromium (Cr(VI))-induced Dermatitis [Zang]	To understand the chemical oxidative mechanisms that underlie the toxicology of Cr(VI), especially the early events during Cr(VI) interaction with skin in the absence and presence of iron sulfate ($FeSO_4$). Guinea pig skin and cultured human skin will be used in this project. A variety of analytical methods will be developed and applied, including spin-trapping electron spin resonance, high-performance liquid chromatography, liquid chromatography/mass spectroscopy, ultraviolet/visible spectrophotometry, fluorescence, and biochemistry methods. The radical species found in skin will be identified. These studies should provide important insight into occupational dermal risk. The results will be helpful to reduce dermal exposure and associated occupational illnesses among construction workers.
Survey of Chemical Exposure Levels in the Biodiesel Production Industry [Law]	To assess occupational health hazards in the emerging industry of biodiesel production. Potential health hazards in terms of exposure to methanol, sodium hydroxide, and soy allergens have been identified by literature searches. Surface and air sampling for these substances in several biodiesel production facilities are proposed. Sources of personnel exposure in the biodiesel production process will be identified and quantified. Results and recommendations from this assessment will be reported to each biodiesel production facility studied, and the overall findings will be distributed through trade and/or peer-reviewed publications.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Computation of Configurational Entropy in Receptor-Ligand Binding: Development of the MIE-NN Method [Hnizdo]	To examine the validity of the mutual information expansion-nearest neighbor (MIE-NN) method to study complex systems and to study chemical systems of occupational interest. One such chemical is a nanoparticle utilized in industry with a cup-like structure that captures smaller molecules such as benzene. The nanoparticle is a valid receptor-ligand system, and this study is consistent with interests in toxicities emerging from nanotechnology. The second system is the estrogen receptor (ER), which is implicated in a number of toxicological mechanisms. MIE-NN is an accurate and tractable method to calculate how toxic molecules, or ligands, bind to biological receptors on large molecules such as proteins, which has been identified. This development has implications in accurately screening chemicals for toxicity. Further development of MIE-NN will furnish the first reliable calculation of entropy costs when ligands bind to receptors.
Blood Gene Expression Profile to Detect Chemical Toxicity [Joseph]	To obtain animal experimental data to support the hypothesis that blood gene expression profiles can be used as specific, sensitive, and non-invasive surrogate biomarkers to predict target organ toxicity resulting from occupational exposure to toxic chemicals in workers. Rats will be treated with target organ-specific toxic chemicals and global gene expression profiles will be analyzed to identify unique blood gene expression signature "fingerprints" that can be used as surrogate markers of target organ specific toxicity. The gene expression signatures will be further validated for their sensitivity to predict target organ toxicity in a preclinical stage. The goal is to develop a simple test that is sensitive to detect pre-clinical toxicity due to occupational exposure to toxic agents among workers. The findings of the project may result in the development of biomonitoring methods for the determination of exposure to toxic agents and health effects in workers.
Neuroinflammation, Glial Signaling, and Neurotoxicity [O'Callaghan]	To characterize novel molecular changes associated with gliosis, a sensitive cellular index of neurotoxicity. A large number of workplace-related chemicals, and the physiological and environmental factors with which they interact, are associated with subtle neurological effects. Establishing the neurotoxicology of these effects is hampered by the lack of available biomarkers of neurotoxicity. Anti-inflammatory and proinflammatory agents will be used to validate the role of neuroinflammation in inducing gliosis and neurotoxicity. These studies will evaluate the utility of neuroinflammatory mediators as early biomarkers of neurotoxicity in preclinical assessments. Expected outcomes include NIOSH guidelines on neurotoxicity assessment.
Protection against Occupational Disease by Xenobiotic-activated Receptors [Ma]	To obtain new insights into the mechanism of receptor-mediated toxic responses to occupational chemicals, and new approaches for designing better strategies to prevent occupational diseases worldwide. Receptor-mediated gene regulation is a major mechanism by which many occupational/environmental chemicals cause toxic effects or diseases, and by which antioxidants protect against occupational disease. Experimental models are examining the roles and mechanisms of action of aryl hydrocarbon receptor, nuclear factor (erythroid-derived 2)-related factor 2, and metal regulatory transcription factor 1 in the toxicity of halogenated and polycyclic aromatic hydrocarbons, chemoprotection by phenolic antioxidants, and responses to toxic heavy metals, respectively. The studies focus on occupational cancer and cardiovascular and reproductive diseases and on risk assessment and chemoprotection.
Induction of Lung Fibrosis by Cerium Oxide in Diesel Exhaust [Ma]	To characterize the potential pulmonary toxicity of exposure to cerium oxide nanoparticles in the absence or presence of diesel exhaust particles (DEP), using a rat model. Exposure to DEP causes respiratory diseases and induces lung cancer. Recently, cerium oxide has been used as a diesel engine catalyst to lower emissions of DEP and some toxic gases; however, cerium oxide nanoparticles have been detected in the diesel emissions. This project will provide the first useful dose-response and time-course information for cerium/diesel. Results should establish cellular mechanisms that are critical to understanding the health effects of cerium oxide and will aid in risk assessment.

NIOSH/NTP [Project Officer]	Objective and Project Summary
Tungsten Carbide–Cobalt (WC-Co) Nanoparticles in Initiating Angiogenesis by Reactive Oxygen Species (ROS) [Ding]	To investigate the potential pulmonary carcinogenesis in response to WC-Co particle exposure using cell cultures and animal models. Exposure to WC-Co causes pulmonary disease and lung cancer. Preliminary results indicated that nanoparticles of WC-Co generated more ROS than did fine particles when incubated with cells. Both fine particles and nanoparticles of WC-Co stimulate angiogenesis. Mechanistic investigations (gene mutation, activation of transcription factors, ROS generation) will be conducted to examine the events of WC-Co-induced tumor initiation, promotion, and progression. Determining the mechanisms involved in WC-Co-induced carcinogenesis in parallel with manipulating target signaling could help develop biomarkers and possible prevention strategies for WC-Co-induced diseases, thus targeting cancer, respiratory disease, and nanotechnology issues.
Potential Biomarkers for Pulmonary Effects from Exposure to Iraq Ambient Air Dust [Vallyathan]	To investigate the toxicity and pathogenicity of ambient dust collected from Iraq using a rat animal model. Some military personnel in Iraq are exposed to high concentrations of ambient air dust containing potentially large concentrations of crystalline silica and other silicates, which could increase risk of lung diseases. Results obtained from these studies may assist in developing early detection biomarkers and implementation of prevention strategies for ambient dust exposure in Iraq. Results will provide an integrated, comprehensive understanding of the toxic mechanisms involved in the development of fibroproliferative risk caused by particulate dust exposure.
Cell-based Assessment for Iron Nanoparticle-induced Health Risks [Qian]	To develop an *in vitro* screening model to assess potential vascular toxicity of nanoparticles and to provide a basis for recommendations and guidance on the safe handling of nanoparticles. The molecular mechanisms by which iron nanoparticles induce enothelial cell permeability changes and produce reactive oxygen species (ROS) in these cells will be studied. The roles ROS play in regulating these cell permeability changes will also be investigated. The hypothesis is that production of ROS plays an essential role in iron nanoparticle-induced endothelial cell damage, which can lead to cardiovascular dysfunction. The research strategies may provide a rapid, inexpensive, *in vitro* alternative to the use of animal models.
Investigation of the Genetic Fingerprint of Chemically-Induced and Spontaneously-Occurring Lung Cancer using a Mouse Model [Reynolds]	To determine if there are different carcinogen-specific chromosomal (genetic) markers in spontaneously-occurring and chemically-induced mouse lung adenocarcinomas. The mice were exposed by inhalation to vanadium pentoxide, nickel oxide, or cumene (a benzene derivative) three chemicals to which workers in the construction and manufacturing sectors are exposed. Mouse lung tumors induced by single- walled carbon nanotubes (SWCNTs) will also be analyzed. Results from these studies will be used to establish biomarkers for early detection and therapeutic intervention of lung cancer in among workers.
Assessment of Carbonaceous Materials on Mutagenicity [Shvedova]	To determine the mutagenic/carcinogenic potential of engineered nanomaterials in the lung. Exposure to ultrafine particles has been linked to respiratory diseases, cardiovascular diseases, and lung cancer. A preliminary study revealed the potential mutagenicity of single-walled carbon nanotubes (SWCNTs) and some hyperplasia in the lungs of tumor-resistant mice exposed to SWCNTs. Data on mechanisms involved in lung cancer development may lead to strategies for early detection in susceptible workers. Data obtained from these studies will address respiratory disease, cancer, and nanotechnology issues and will be used by regulatory agencies (OSHA and EPA) and industry for hazards identification, risk assessment, and management of occupational exposures.
Nanoparticle Properties and Mechanisms Causing Lung Fibrosis [Rojanasakul]	To investigate potential fibrogenicity of carbon nanotubes (CNTs) using both *in vitro* and *in vivo* approaches. The *in vitro* potency sequence of CNTs of different diameters, aspect ratios, or dispersion status will be compared with their fibrogenic potential *in vivo*. These results will provide key information about the fibrogenic mechanisms of CNTs and validate a set of *in vitro* screening assays to predict the fibrogenic potential of nanoparticles.

NCTR/NTP

NCTR/NTP

The National Center for Toxicological Research (NCTR), the FDA's research center, plays a critical role carrying out the agency's mission. NCTR, in partnership with researchers from elsewhere in FDA, other government agencies, academia, and industry, provides innovative technology, methods development, vital scientific training, and technical expertise. The unique scientific expertise of NCTR is critical in supporting FDA product centers and their regulatory roles. NCTR conducts an array of studies that reflect the NTP mission statement.
These NCTR/NTP studies, funded by NCTR voluntary allocations, are listed in Table 4.

Table 4: NCTR/NTP Projects in FY 2009*

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Effects of Caloric Restriction on Rat Testicular Tumor Formation [Leakey]	To investigate the effects of caloric restriction, aging, and circadian time-point on testicular lipocortin 1 levels.
Caloric Restriction and Gene Expression in Agouti Mice [Beland]	To determine how calories modify the development of cancer in mice and the mechanism underlying cancer development in humans.
The Evaluation of Selected Benzodiazepine and Antihistamine Drugs in the Neonatal Mouse Tumorigenicity Bioassay and in Transgenic Human Lymphoblastoid Cells [Fu]	In this study neonatal B6C3F1 mice are dosed at 2 days early in development with the test article, and hepatocarcinogenesis evaluated after 1 year. In addition, the mutagenicity in transgenic human lymphoblastoid cells is examined.
DNA Adducts of Tamoxifen [Beland]	The nonsteroidal antiestrogen tamoxifen, which is currently being used in clinical trials as a chemoprotective agent against breast cancer, has been associated with induction of certain malignancies. In order to determine if tamoxifen is acting through a genotoxic mechanism, this project will characterize DNA adducts from suspected tamoxifen metabolites and develop methods for their detection and quantitation.

**Funded by NCTR voluntary allocations*

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Photoinduction of Cutaneous Malignant Melanoma in TP-ras/ink4A (+/-) Transgenic Mice [Tolleson]	(1) To characterize photochemical DNA damage in the skin of TP-ras/ink-4a mice exposed to UVA+UVB radiation, (2) to determine whether cutaneous malignant melanoma can be induced in neonatal TP-ras (+) ink4a (+/-) transgenic mice using UVA+UVB radiation, (3) to identify photochemically induced mutations within the ink4a/p16/CDKN2A and p53 loci in tumor tissues, and (4) to determine whether UVA+UVB exposure at an early age creates a greater risk for developing cutaneous melanoma in TP-ras (+)ink4a(+/-) mice compared with chronic UVA+UVB exposure of older animals.
Mechanisms and Consequences of DNA Damage and Methylation Dysregulation during Rat Hepatocarcinogenesis [Pogribny]	(1) To confirm that the presence of uracil and abasic sites in preneoplastic DNA from folate/methyl deficient rats creates nonproductive high affinity binding sites for the DNA methyltransferase that compromise normal DNA methylation at the replication fork resulting in genome-wide hypomethylation and (2) to determine whether the double-stranded loss of cytosine methylation is maintained in folate/methyl-deficient rats after nutritional repletion of methyl donors or whether the original methylation pattern and chromatin structure can be reestablished.
Effect of p53 Genotype on Gene-Expression Profiles in Mice Exposed to the Model Mutagen, *N*-Ethyl-*N*′-Nitrosourea (ENU) [Morris]	(1) To determine the effect of mutation in the p53 tumor suppressor gene on gene-expression profiles in young and aged mice, and (2) to determine the effect of mutation in p53 tumor-suppressor gene on gene-expression profiles in young and aged mice exposed to the model mutagen ENU.
Determining the Neurotoxic Profile – Specific Changes in Cortical Gene Expression Resulting from Amphetamine Exposures: A Laser Capture Microdissection- and cDNA Array-Assisted Research [Bowyer]	(1) To determine the importance of the innervation of the dopaminergic and glutamatergic neurotransmitter systems in the neurodegeneration produced in the interneurons in parietal cortex layers II and IV using specific antagonists and agonists of these two systems, (2) to determine the gene expression pattern changes that occur in parietal cortex layers II and IV when AMPH-induced neurodegeneration is produced under normothermic, 2-day AMPH exposure, conditions using cryostat-assisted dissection, and (3) to analyze the changes in gene expression in parietal cortex layers.
Methods for Support of a Functional Proteomics Facility at NCTR [Yu]	(1) To establish and standardize for routine use procedures for whole cell and subcellular organelle isolation for a variety of tissues; (2) to develop and standardize specific and sensitive markers of cell type and organelle purity and yield; (3) to identify, adapt, develop, and standardize appropriate 2-D protein separation technique; and (4) to integrate results of objectives 1-3 to provide "front-end" components of a functional proteomics facility.
Transgenic Mouse Model for Detecting *In Vivo* Mutation Using a Green Fluorescent Protein Reporter [Dobrovolsky]	(1) To produce two lines of transgenic mice expressing the tetracycline-repressor protein, (2) to investigate the efficiency of *in vivo* repression of green fluorescent protein (GFP) in various tissues of different lines of the double-transgenic mice, and (3) to determine the frequency of spontaneous and gamma-ray induced TetR mutation in lymphocytes of double-transgenic mice using flow cytometry.
Analyses of the Rat Hippocampus via DNA Microarrays and a Novel Antibody Array, Coupled with Laser Capture Microdissection (LCM) – Evaluation of the Effect of Aging on Gene and Protein Expression Associated with Learning [Patterson]	(1) To measure gene and protein expression in regions of the hippocampus to determine regional distribution; (2) to determine the effect of aging on regional distribution of hippocampal proteins in three strains of rats; (3) to determine if aging, behavioral performance, and alterations in gene and protein expression in the hippocampus are related; and (4) to correlate the differences in gene and protein expression with behavioral performance of young adult and aged rats in a learning task previously shown to be sensitive to changes in protein expression.
Sulfotransferase 1A1 (SULT1A1) Genotype and Phenotype in Relation to Efficacy of Tamoxifen Treatment [Ning]	(1) To determine whether induction of SULT1A by 4-OH TAM results in an increase in expressed protein and enzymatic activity toward environmental estrogens in tamoxifen treated breast cancer patients, (2) to determine the effect of 4-OH TAM on SULT1A1 activity in breast cancer cell lines, and (3) to determine SULT1A1 genotype in tamoxifen-treated women and genotype-phenotype correlations.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Assessment of Depression Risk Associated with Accutane (13-cis-Retinoic Acid or Isotretinoin) and All-Trans-Retinoic Acid Treatment: Measurement of Behavioral and Neurochemical Alterations in Adult Sprague Dawley and Flinders Sensitive and Insensitive Line Rats [Ferguson]	(1) To establish oral doses of 13-cis-retinoic acid and all-trans-retinoic acid in rats that produce peak plasma levels similar to those of humans prescribed 13-cis-retinoic acid, (2) to measure the toxicity and pathology associated with long-term oral treatment with 13-cis-retinoic acid and all-trans-retinoic acid in rats, (3) to describe the behavioral alterations associated with chronic 13-cis-retinoic acid and all-trans-retinoic acid treatment in adult male and female Sprague Dawley rats, (4) to determine if such alterations resemble those described in humans treated with 13-cis-retinoic acid, (5) to measure sex differences in behavioral response to 13-cis-retinoic acid and all-trans-retinoic acid treatment, (6) to evaluate the reversibility of the 13-cis-retinoic acid-induced and/or all-trans-retinoic acid-induced alterations, (7) to assess if genetic predisposition to depression determines the frequency and/or magnitude of the behavioral alterations associated with 13-cis-retinoic acid and/or all-trans-retinoic acid treatment, and (8) to quantitate the neurochemical alterations induced by 13-cis-retinoic acid and/or all-trans-retinoic acid treatment.
Effect of Soy-Containing Diets on Ammonium Perchlorate-Induced Thyroid Toxicity in Sprague Dawley Rats [Doerge]	To determine the effect of dietary soy and genistein, the principal soy isoflavone, on the dose-response characteristics for perchlorate-induced thyroid toxicity in male Sprague Dawley rats.
Global and Locus-Specific DNA Hypomethylation: A Common Mechanism Involved in Genotoxic and Non-Genotoxic Rat Hepatocarcinogenesis [Pogribny]	(1) To determine if the temporal alterations in the genomic methylation profile in preneoplastic liver tissue observed in the folate/methyl-deficient model of rat endogenous hepatocarcinogenesis also occur in other carcinogenesis models, (2) to identify genes that are consistently up-regulated or down-regulated in target tissue during the promotion stage of carcinogenesis, and (3) to evaluate whether or not the global and locus-specific DNA hypomethylation, along with aberrant expression of related genes and changes in chromatin conformation, is specific only to target tissues and may be used for early detection.
Carcinogenicity of Acrylamide and its Metabolite, Glycidamide, in Rodents: Neonatal Mouse Bioassay [Beland]	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice treated neonatally.
Biomarkers of Liver Disease and Toxicity [Beger]	To develop biomarker profiles for normal individuals and those with liver diseases or toxicity.
Assessment of Ketamine in the Developing Nonhuman Primate [Wang]	(1) To determine, using neurohistochemical approaches, if, and at what developmental stages, ketamine exposure increases neuronal apoptosis/proliferation; (2) to determine, using neurohistochemical approaches, the dose-response for ketamine to produce apoptosis at the most sensitive developmental stage; (3) to determine the reversibility or permanence of the response using behavioral, imaging, and neurohistochemical approaches; and (4) to determine, at the most sensitive stage and dose, genomic and proteomic responses to ketamine treatment.
Phytoestrogens and Aging: Dose, Timing, and Tissue [Doerge]	To evaluate the potential benefits or detrimental effects of dietary phytoestrogens on breast cancer progression, adipose tissue, and the brain, using well-established laboratory animal models.
Development of a Physiologically based pharmacokinetic/pharmacodynamic (PBPK/PD) Model for Acrylamide [Doerge]	(1) To develop a PBPK/PD model for acrylamide and its metabolite glycidamide, (2) to determine mutagenicity of acrylamide and glycidamide in Big Blue rats, and (3) to determine DNA adduct levels and the extent of mutagenicity of furan and its metabolite cis-2-buten-4-dial in neonatal B6C3F1/Tk+/- mice.
Optimal Tree-Based Ensemble Methods for Class Prediction [Chen]	(1) To build on the novel Decision Forest classification model developed at NCTR to produce an ensemble of decision trees, each constructed from a different set of predictors, by statistically pruning to optimal size using cross-validation, and (2) to use Monte Carlo simulation techniques to compare the performance of the proposed decision forest classifiers to the performance of a single optimal decision tree. A primary area of application is the classification of subjects into risk categories in class-prediction problems occurring with genomics and proteomics data.
Microbial Degradation of Fluoroquinolone Antimicrobial Agents [Sutherland]	To identify microorganisms that either completely degrade fluoroquinolones or modify the fluoroquinolone molecule so as to reduce its toxicity to bacteria.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Evaluation of the Genetic Toxicity and Behavioral Effects of Chronic Methylphenidate Exposure in Juvenile Male Rhesus Monkeys *(Macaca mulatta)* [Morris]	(1) To determine the baseline frequency of genetic damage in a population of juvenile rhesus monkeys, (2) to determine the frequency of those measures of genetic damage in a population of juvenile rhesus monkeys at defined intervals during a chronic exposure to methylphenidate, (3) to determine if chronic exposure to methylphenidate results in measurable effects on the behavior of juvenile rhesus monkeys utilizing the NCTR Operant Test Battery, and (4) to determine the plasma concentration of methylphnidate and its major metabolite retalinic acid during chronic exposure of juvenile rhesus monkeys to the drug.
Evaluation of the Genotoxicity and Pharmacokinetics of Methylphenidate in Male Big Blue® Mice [Manjanatha]	(1) To determine the metabolites of methylphenidate soon after exposure in B6C3F1 mice in order to compare the major metabolites in the human, monkey, and mouse; (2) to determine the plasma levels of methylphenidate and its major metabolites in the B6C3F1 mouse after 28 days of exposure; (3) to determine the effect of exposure to methylphenidate on body and organ weights of the B6C3F1 mouse after 28 days of exposure; (4) to determine if long-term exposure to methylphenidate results in a dose-responsive increase in the liver c11 gene mutant frequency of Big Blue® mice; and (5) to determine the pharmacokinetics of methylphenidate and its major metabolite ritalinic acid in B6C3F1 mice.
Biotransformation of Isoflavonoid Phytoestrogens by Colonic Microfloras of Experimental Animals [Rafii]	To use fecal samples of monkeys and rodents to determine if the metabolites produced by intestinal microflora of experimental animals exposed to phytoestrogens are the same as those of humans or whether animal-colonic bacteria metabolize them to different compounds. This information is necessary for extrapolation to humans of the data obtained from treatment of animals with phytoestrogens.
Molecular Mechanisms Underlying Gender-Associated Differences in the Adverse Reactions to the Antiretroviral Agent Zidovudine (AZT): Role of Mitochondrial Toxicity [Desai]	To elucidate molecular mechanisms of mitochondrial dysfunction that will address gender-based differences in adverse effects of antiretroviral drugs, such as AZT.
Neurotoxicity Assessment of Manganese (Mn) Nanoparticles in PC-12 Cells and in Mice [Ali]	(1) To evaluate the neurotoxicity of different-sized manganese nanoparticles using PC-12 cultured cells; (2) to determine if *in vitro* exposure to Mn nanoparticles selectively induces specific genomic changes in PC-12 cultured cells using oligonucleotide microarrays; (3) to determine if multiple doses of Mn nanoparticles produce reactive oxygen species (ROS), alterations in lipid peroxidation and/or changes in antioxidant enzymes and glutathione levels in various regions of the mouse brain; (4) to determine if single or multiple doses of Mn-nanoparticles induce specific genomic changes, neurotransmitter levels, 3-nitropyrosine in various regions of the mouse brain using oligonucleotide microarrays; and (5) to determine if multiple doses of Mn-nanoparticles produce morphological alterations in the brain and other visceral organs of the mouse.
Ketamine Pharmacokinetics in Children [Doerge]	To develop and validate a sensitive liquid chromatography/tandem mass spectrometry (LC/MS/MS) method to quantify the enantiomers of ketamine and nor-ketamine in plasma from children dosed with racemic ketamine during surgical procedures. These measurements will be the basis for pharmacokinetic evaluation of ketamine and nor-ketamine enantiomers in children.
The Effects of Acrylamide and PhIP on Normal Human Brain Cortical Neuronal (HCN-1), PC12, and HepG2 Cells: Activation or Inactivation of Phase I and II Enzymes [Ali]	(1) To determine the effects of acrylamide and/or PhIP on cell proliferation, transformation, toxicity, apoptosis, and neurotransmitter turnover in HCN-1 and PC12 cells; (2) to determine the effects of acrylamide and/or PhIP on the expression of CYP 1A1, 1A2, 1B1, 3A4, and glutathione-S-transferases in HepG2, PC12, and HCN-1 cells; and (3) to determine whether the dietary agents I3C and sesame seed lignans modulate the effects of acrylamide and/or PhIP.
Cancer Mutations as Biomarkers of Cancer Risk: Human Studies with Implications for Personalized Medicine [Parsons]	(1) To develop information necessary for the rational use of oncogene mutations as quantitative biomarkers of cancer risk; specifically Allele-Specific Competitive Blocker polymerase chain reaction (ACB-PCR) will be used to determine normal and pathological levels of relevant oncogene mutations in multiple human tissues and tumors, (2) to compare the information derived from human tissues with data generated in a parallel rodent protocol as an approach for incorporating carcinogenesis-relevant data into the rodent to human extrapolation necessary in cancer risk assessment, and (3) to validate a streamlined ACB-PCR methodology and develop the methodology necessary to measure oncogene mutant fraction in cell-free DNA isolated from plasma.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Liver Toxicity Biomarkers Study: Phase 1, Entacapone and Tolcapone [Beland]	To establish liver toxicity biomarkers and associated algorithms for use in preclinical drug development that will predict the probability of occurrence of hepatocellular injury at any subsequent phase of drug development or following approval of the drug for marketing. Emphasis will be placed upon drugs that do not demonstrate classical signs of liver toxicity during preclinical stages of drug development.
Evaluating the Utility of ACB-PCR in Dose-Response Assessment and Mode-of-Action Evaluation [Parsons]	To further develop, evaluate, and disseminate the ACB-PCR method and to determine whether ACB-PCR measurements of specific oncogenic base substitutions can be used to inform and improve the dose-response and mode-of-action assessments required in cancer risk assessment.
Mechanisms of Gender Differences in Aspirin Effects: Metabolizing Enzymes and Therapeutic Targets [Ning]	(1) To profile gender differences in the mRNA expression and protein production of drug-metabolizing enzymes known to be involved in aspirin metabolisms using human liver; (2) to characterize molecular mechanisms of sex hormones (estrogens, progestogens, and androgens) in regulation of the expression of aspirin-metabolizing genes in human ER-positive hepatic-cell line HepG2-ER(+); (3) to measure sex-hormone modulation of aspirin's effect on platelet aggregation and its related biomarkers [cyclooxygenase (COX)-1, COX-2, prostaglandin 2, thromboxane A2, and leukotriene B4] using human platelet precursor cells; (4) to identify cell lines, by measuring prostacyclin dynamics (prostaglandin 2, thromboxane A2, and leukotriene B4) and expression of aspirin-targeting enzymes [COXs, nitric oxide synthase (NOS), and lipoxygenase]; and (5) to evaluate sex-hormone modulation of response to aspirin in apoliprotein E-deficient mice.
Sex Differences in Drug Abuse Susceptibility in Methylphenidate (MPH)-Treated Rats [Ferguson]	To determine potential sex differences in substance abuse susceptibility after methylphenidate (Ritalin) treatment during adolescence. The hypothesis is that male and female rats treated with methylphenidate will exhibit different levels of drug abuse susceptibility.
Histochemical Test Battery for Evaluating the Efficacy and Toxicity of Putative Alzheimer's Disease Therapeutics of FDA Relevance [Schmued]	To test the hypothesis that Alzheimer's disease (AD), which is characterized by the deposition of insoluble amyloid plaques in the brain, is the result of a cascade of pathological processes and that pharmacological intervention at various points within this sequence of events could attenuate the resulting pathology.
Behavioral Phenotype of the Tg.AC Mouse [Ferguson]	To quantify behaviors of the transgenic mouse strain Tg.AC. Behaviors of the parent, hemizygous, and homozygous strains will be compared.
Neurotoxicity Assessment of Silver (Ag) Nanoparticles in PC-12 Cells and in Rats [Ali]	(1) To evaluate the neurotoxicity of different sizes of Ag nanoparticles using cultured PC-12 cells; (2) to determine if *in vitro* exposure to Ag-nanoparticles selectively induces specific genomic changes in cultured PC 12 cells using microarrays; (3) to determine if single or multiple doses of Ag nanoparticles produce ROS, alteration in lipid peroxidation and/or changes in antioxidant enzymes (catalase, superoxide dismutase, glutathione peroxidase) and glutathione levels in the rat brain; (4) to determine if single or multiple doses of Ag nanoparticles induce specific genomic changes, neurotransmitter, or 3-nitrotyrosine in the rat brain; and (5) to determine if multiple doses of Ag nanoparticles produce morphological alterations in blood-brain barrier, brain, or other visceral organs of the rat.
Assessment of Gaseous Anesthetics in the Developing Nonhuman Primate [Wang]	(1) To evaluate dose-response effects of gaseous anesthetics by determining if prolonged exposure to nitrous oxide or isoflurane alone will result in an increase in neuronal cell death or prevent or enhance each other's effects on the developing nonhuman primate; (2) to determine if a relatively high dose or prolonged exposure of the developing nonhuman primates to nitrous oxide or isoflurane alone, or their combination will induce long-term behavioral deficits, as well as long-lasting pathological changes, as determined by non-invasive imaging techniques [high resolution dedicated positron emission tomography (microPET) and MRI]; and (3) to identify potential underlying mechanisms that could link alteration of mitochondrial function and elevation of ROS to gaseous anesthetic-induced neuronal cell death using L-carnitine as an injury modulator.
Evaluation of Growth and Pubertal Development in Male Rhesus Monkeys (Macaca mulatta) Chronically Exposed to Methylphenidate Hydrochloride (MPH) [Morris]	To study dosing with methylphenidate hydrochloride through the completion of puberty to evaluate of changes in pharmacokinetics and operant behavior testing.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Laboratory Studies in Melamine and Cyanuric Acid Biochemical Toxicology [Tolleson]	To determine chemical and biochemical properties of melamine and cyanuric acid that may influence their toxicity and retention as tissue residues.
Assessment of Effects and Metabolism of Synthetic Azo Colorants Used in Women's Cosmetics on Human Skin Microbiota [Chen]	To evaluate the metabolism and effect of color additives used in cosmetics on the skin microbiota. Specific objectives are (1) assessment of the degradability of the synthetic azo colorants in cosmetics by skin bacteria, (2) identification and quantification of the potential carcinogenic and toxic aromatic amines in the metabolites, (3) evaluation of the effects of exposure of a predominant skin bacterium *Staphylococcus aureus* to cosmetics using 'omics' approaches, and (4) use of an *in vitro* bio-engineered human skin tissue model applied with the appropriate levels of skin surface bacteria to evaluate the effect of cosmetics on skin microbial ecology.
Genotyping of Transporter Genes Associated with Gender Differences and Promoter Methylation of UGT1A1 in Human Liver: A Means of Assessing Safety and Toxicity of Chemotherapeutic Drugs [Lynn-Cook]	(1) To identify polymorphisms in drug transporter genes identified to be differentially expressed according to gender in human liver samples, (2) to correlate polymorphism frequencies in males and females to gene expression, (3) to evaluate the methylation profile of UGT1A1 promoter in human liver samples from males and females and correlate it to expression of UGT and its activity, and (4) to evaluate effects of polymorphisms in transporter genes on uptake and clearance of chemotherapeutic drugs in a functional assay using the B-CLEAR human *in vitro* model.
Mechanistic Study of Glitazone (TZD)-Induced Hepatotoxicity by Integrating Gene Expression and Metabolic and Proteomic Profiles [Guo]	(1) To evaluate *in vitro* hepatotoxicity of anti-diabetic TZDs including troglitazone, ciglitazone, rosiglitazone, and pioglitazone; (2) to identify gene expression signatures associated with effects of treatment by TZDs; (3) to measure synthesis profiles of metabolites (nontargeted) and the turnover of specific metabolites involved in some liver cell specific metabolic pathways; (4) to measure liver-specific proteins in cell culture media and quantify the turnover rate of some liver-specific membrane enzymes; (5) to identify enriched genes, metabolites and proteins responsible for separating and correlating the toxicity endpoints; (6) to integrate data to reconstruct pathways and networks using existing computational models such as hierarchical approaches or new models to be developed; and (7) to identify genes, processes, and biomarkers associated with TZD-induced toxicity.
Interaction of Dietary Resveratrol with Intestinal Microflora [Sutherland]	(1) To identify how resveratrol alters the population dynamics of the human intestinal microbiome and thus affects overall health, (2) to determine how the microorganisms affect resveratrol bioavailability, (3) to develop a model system for bacterial interactions with dietary supplements, and (4) to understand the effect of resveratrol on intestinal microbial community dynamics.
Benzocaine-Induced Methemoglobinemia in an Acute Rat Model [Beland]	To determine the dose-effect of benzocaine-induced methemoglobinemia in rodents.
Chemical Inactivation of Protein Toxins on Food Contact Surfaces [Tolleson]	(1) To identify cleaning/sanitizing treatments that result in elimination and/or inactivation of protein toxins (abrin and ricin) on food-contact surfaces, (2) to identify surrogate(s) that can be used to study chemical inactivation of abrin or ricin, and (3) to measure the loss of ricin and abrin biological and biochemical activities in the presence of cleaning/sanitizing solutions using RAW264.7 macrophage cytotoxicity assays and 28S rRNA adenosine *N*-glycosidase RTqPCR-based enzyme assays.
Evaluating the Effects of Over-the-Counter Skin Products, such as Sunscreen, on the Absorption of Dermally Applied Estradiol, in an *In Vitro* and *In Vivo* Model [Gopee]	(1) To investigate the pig as an animal model that will allow the measurement of systemic estradiol, when applied dermally, (2) to use the animal model to mimic the clinically reported effects of sunscreen application on estradiol absorption from topically applied estradiol products, (3) to evaluate factors such as components in sunscreens or time of application on the rate and extent of estradiol absorption from dermally applied products, and (4) to develop an *in vitro* system study and determine the individual components or combination of components in sunscreens responsible for the enhancement in the absorption of estradiol from topically applied estradiol products.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Method Development for Study of Antioxidant Properties in Dietary Supplements [Fu]	**Microsomal metabolism-mediated studies:** To determine if herbal dietary supplements can alter microsomal-mediated free-radical formation or lipid peroxidation. **Cell culture studies:** To determine the toxic effects of herbal dietary supplements on A549 human lung carcinoma cells and rabbit brain rBCECs cells by (1) measuring mitochondrial dehydrogenase activity, intracellular ROS concentration and mitochondrial membrane potential and (2) conducting electron spin resonance spectroscopy measurement of lipid peroxidation.
Isolation and Characterization of Fluoroquinolone-Resistant Bacteria from Shrimp [Nawaz]	(1) To isolate and identify fluoroquinolone-resistant Gram-negative bacteria from shrimp imported from different countries, (2) to perform molecular characterization of fluoroquinolone-resistant determinants, and (3) to perform molecular typing of fluoroquinolone-resistant bacteria.
Evaluation of Molecular Changes in Formalin-Fixed Paraffin-Embedded Prostate from NCTR CD (Sprague Dawley) Rats Treated with Ethinyl Estradiol and Genistein [Delclos]	To evaluate the prostate tissue, stored in paraffin blocks, for molecular changes reported to be induced in the prostate by estrogens and lead either directly to later lesions or sensitization of the tissue to later hormone challenge.
Evaluation of the Applicability of Standard Assays to Genotoxicity of Engineered Nanomaterials [Chen]	To evalutate the activity of four nanoscale materials thought to represent the most common nanomaterials for which human exposure may be expected: nanoscale carbon nanotubes, titanium dioxide, nanoscale gold, and nanoscale silver in three standard tests required by the FDA (*Salmonella* Ames test, mouse lymphoma assay, *in vivo* mouse micronucleus assay) and in a new transgenic mutation system (Big Blue® and gpt-delta hybrid transgenic mouse).
Effect of Urinary pH upon the Nephrotoxicity of a Combined Exposure to Melamine and Cyanuric Acid [Beland]	To determine the effect of urinary pH upon the renal toxicities elicited by a combined exposure of melamine and cyanuric acid.
Assessment of the Nephrotoxicity of a Seven-Day Combined Exposure to Melamine and Cyanuric Acid [Gamboa Da Costa]	To investigate the nephrotoxic effect of a seven-day co-exposure to melamine and cyanuric acid in Fischer 344 rats.
Biomarkers of Liver Toxicity [Salminen]	(1) To discover biomarkers of hepatotoxicity in preclinical studies that are more predictive of adverse effects in humans, (2) to qualify the identified biomarkers (e.g., via the FDA/European Medicines Agency qualification process), and (3) to determine their potential translation for clinical use.
Interaction of Botanical Silymarin with Intestinal Microflora [Khan]	(1) To identify how Silymarin (milk thistle) alters the population dynamics of the human gastrointestinal microbiota, (2) to determine how the predominant human intestinal microorganisms affect Silymarin bioavailability and activity, (3) to develop a model system for bacterial interactions with dietary supplements whereby the microbial perturbations caused by Silymarin can be monitored and the metabolism of this compound by microbiota can be detected, and (4) to determine the dynamics of the human intestinal microbiota with Silymarin using real-time PCR or other molecular techniques.
Preclinical Metabolomic Investigation of Drug Pharmacokinetics in Multiple Drug Toxicity Studies [Sun]	(1) To apply metabolomic methods to investigate a drug-metabolite profile in urine samples from preclinical studies using LC/MS and NMR with the combination of principal component analysis (PCA) and heterocorrelation analyses of NMR and MS data, (2) to determine the excretion kinetics of the drug-*N*-acetyl-cysteine conjugates and S-adenosylmethionine using LC/MS/MS technique, and (3) to investigate mercapturic acids profile using a highly sensitive and selective constant neural-loss technique developed on a triple quadrupole mass spectrometer.
Development of Predictive Mitochondrial Biomarkers for Drug-induced Cardiotoxicity using a Systems Biology Approach [Desai]	(1) To identify molecular biomarkers useful in preclinical, as well as clinical, studies to predict harmful effects of drugs on the heart, and (2) to determine the efficacy of a cardio-protective agent against drug-related toxicity.

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Development of Cancer-Relevant Biomarkers for Identification of Potential Carcinogens: Research to Understand the Normal Background Frequencies in Rats [McKinzie]	To use the ACB-PCR assay to measure levels of cancer-associated mutations in normal rodent tissues, and (2) to generate a database of mutation measurements in various rat tissues, at various ages, and in two strains of rat with different genetic backgrounds for different human-relevant oncogene mutations to establish which mutations are useful as biomarkers of cancer. This database can be used to compare and normalize the background mutation frequencies in rat to the background frequencies observed in homologous human proto-oncogenes and tumor suppressor genes.
Inactivation of UDP-Glucuronosyltransferases (UGT) in Human Breast Tissues: Assessing Cancer Risk and Tamoxifen Safety and Toxicity [Starland-Davenport]	(1) To characterize UGT mRNA expression in normal and malignant human breast tissues isolated from the same donor and from different donors, to screen for inter-individual differences in UGT expression and determine the association of UGT expression and breast cancer risk; (2) to identify polymorphisms in UGT genes that show significant inter-individual differences in UGT mRNA expression in all breast tissues; (3) to determine the methylation profile of those UGTs identified in objective 2 and correlate it to UGT expression; and (4) to determine the effects of polymorphisms in UGT genes on glucuronidation of estradiol-17 beta, 4-OH-E1, and 4-hydroxy-Tamoxifen (4-OH-TAM) using glucuronidation activity assay and 3-(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide cytotoxicity assays.
Interagency Collaboration on Identification of *In Vitro* and Omics Biomarkers for Liver Toxicity [Tong]	(1) To develop a battery of mechanistically informative *in vitro* and omics assays for developing novel biomarker identification models and methods to improve safety and risk assessment of hepatotoxicity, and (2) to identify novel biomarker identification methods tailored to specific mechanisms of liver toxicity. **Phase I:** The common set(s) of compounds from the FDA Liver Toxicity Knowledge Base, the EPA ToxCast, the NCGC -NTP -EPA Tox21, and the CDC HazDat and HSEES databases will be identified as a test case to assess the current gaps of the existing data and further assay needs for development and validation/verification of biomarker identification models and methods. **Phase II:** A new set of compounds will be further identified for study in the Liver Toxicity Knowledge Base, ToxCast, and Tox21 to improve the robustness and reliability of models for regulatory application.
Collaborative Inter-Agency Development of *In Silico* Computational Toxicology Modeling to Predict Adverse Drug/Chemical Interactions with Cytochrome P450 Enzymes [Beger]	(1) To develop *in silico* computational models to predict chemical interactions that can inhibit CYP3A4 and CYP2D6 enzymes, and (2) to use several different modeling methods to model compound-compound-enzyme interactions since each modeling technique has strengths and weaknesses over other modeling techniques.
3D- and 4D-QSDAR Modeling Applied to Various Toxicological Endpoints [Beger]	(1) To develop models using 3D- and 4D-QSDAR models for endocrine disruptors, lowest-observed-adverse-effects level (LOAEL) and no observed-adverse-effects level (NOAEL) and other relevant toxicological endpoints; (2) to test training models with external test sets; (3) to compare the training and testing results to previous QSDAR, quantitative structure-activity relationship QSAR, and SAR models; and (4) to determine how the technique used to predict 13C or 15N NMR spectra effect3 D-QSDAR modeling.
Relationship between Liver Epigenetic Phenotype and Susceptiblity to Nonalcoholic Steatohepatitis-Induced Hepatocarcinogenesis in Mice [Pogribny]	(1) To determine the role of epigenetic dysregulation in the etiology and pathogenesis of dietary non-alcoholic steatohepatitis (NASH)-induced hepatocarcinogenesis in mice, (2) to determine whether intrastrain-specific susceptibility of mice to NASH-induced hepatocarcinogenesis is associated with differences in individual hepatic epigenetic phenotypes, (3) to determine the role of epigenetic dysregulation in the etiology and pathogenesis of NASH-induced hepatocarcinogenesis in mice induced by tamoxifen administration, and (4) to determine whether aberrant epigenetic markers can be used as targets for prevention of NASH-induced hepatocarcinogenesis in mice.
Methods Development for Toxicity Assays Using The Zebrafish Embryo as a Model System: Whole Animal High Throughput Assays For Chemical Testing [Kanungo]	(1) To establish a high throughput assay system using Zebrafish embryos for toxicity assessments of FDA-relevant compounds, and (2) to focus on establishing a high throughput screening assay to monitor both traditional morphological and behavioral endpoints of toxicity and the newer, more subtle organ-specific toxicities.
Rapid Detection of Ribosome-Inactivating Protein Toxins In Foods [Tolleson]	To provide robust methods for detecting the biological activity of the potential bioterrorism agents ricin, abrin, and shiga-like toxins, each of which is characterized as a ribosome inactivating protein (RIP) toxin, in three selected foods (spinach, apple juice, and milk).

NCTR/NTP Project [Project Officer]	Objective and/or Project Summary
Effect of Pediatric Anesthetics on Zebrafish Embryos: Neurotoxicity versus Gene Expression Changes and Neuronal Kinase (Cdk5) as a Mediator of Toxicity [Kanungo]	(1) To determine whether ketamine will have neurotoxic effects (on neurogenesis and axonogenesis) in zebrafish, and (2) to determine if the window of such effects varies between early and late differentiating neurons (sensory and motor neurons, respectively).
Long Term Consequences of Neonatal Ketamine Anesthesia in Rhesus Monkeys: Extended Cognitive Assessments [Paule]	(1) To continue monitoring the cognitive capabilities of rhesus monkey subjects that were exposed to a single, 24-h bout of ketamine-induced anesthesia during the first week of life and (2) to extend the functional domains that are being assessed on the developing subjects to include temporal discrimination task, counting task, and reversal learning task.
Study of Nanoparticle Migration from Food-Contact Nanomaterials: Characterization and Quantification of Silver Nanoparticles [Trbojevich]	To develop analytical methods to study the migration, presence, and concentration of nanoparticles from food package materials.
Real-Time PCR Assays for Ricin and Related Potential Bioterrorism Agents in Food [Melchior]	(1) To develop the precise materials and methods needed to perform the proposed assays; (2) to test the PCR assays for simplicity, rapidity, and reliability; and (3) to test whether the assays function in real-world situations, such as with contaminated food.
Developmental Toxicity of Environmental Contaminants in Folate-Deficient Mice [Hansen]	To test the hypothesis that environmental conditions may cause suboptimal delivery of folic acid to the fetus, which can result in birth defects.
Training for Bisphenol-A Studies [Ferguson]	To study the effect of bisphenol-A exposure on complex behavioral assessments and quantitative volumetric analysis of sexually dimorphic brain regions in the rat.
Analysis of Blood Pyruvate and Valproic Acid Toxicity in Wistar Han Rats in Response to Dietary Carbohydrate and Calorie Restriction with High Fat, Moderate and Low Carbohydrate Diets [Beger]	(1) To develop an *in vivo* rat model with lower plasma pyruvate levels by using dietary carbohydrate restriction, (2) to determine whether pyruvate blood levels in caloric-restricted rats fed a high fat/low caloric diet are decreased relative to rats fed a balanced diet, (3) to determine survival of Wistar Han rats on high fat/low caloric diet, and (4) to assess susceptibility of Wistar Han rats on high fat/low caloric diet to valproic acid-induced liver injury.
Preliminary Study to Determine the Physiological and Cardiovascular Effects of Citru Aurantium in Mini-Pigs [Hansen]	(1) To develop procedures for implantation of telemetry monitors in minipigs; (2) to determine the best method for collecting physiological and cardiovascular variables by telemetry in minipigs; and (3) to determine the best method for dosing minipigs with extracts.
Development of C57BL6 Mouse Colony with Specific Transgene [Manjanatha]	To develop transgenic strains of C57BL6 bearing transgenes designed for the detection of *in vivo* mutagenic events.
NCTR/ARL-ORA Nanotechnology Core Facility [Howard]	To provide analytical support to research divisions in the area of nanotechnology characterization and detection.
Analytical Assay for Photochemical Generation of Hydroxyl Radical [Howard]	To develop quantitative methods to monitor the production of hydroxyl radical following UV irradiation of nanoparticles in suspension.

NIEHS/NTP

NIEHS/NTP

Photo courtesy of Steve McCaw

NIEHS/NTP Leadership

The NTP and NIEHS underwent a change in leadership as Dr. Linda S. Birnbaum assumed the position of Director of the NTP and the NIEHS, replacing Acting Director Dr. Samuel Wilson. The appointment was announced on December 3, 2008 by Dr. Raynard Kington, acting director of the NIH. Dr. Birnbaum began her new positions on January 19, 2009, and was formally installed in a ceremony on March 12, 2009. At that ceremony she presented a vision for new opportunities and advances in environmental science and toxicology at the NIEHS and NTP. Dr. Birnbaum has described the new and renewed emphasis for the NTP in many areas, including:

- coordinating toxicity testing across the Federal government
- developing new methodologies for efficient and thorough toxicological assessments
- establishing additional capacity for tests involving dosing during the perinatal period
- increasing understanding of exposure-response relationships and issues of dosimetry
- developing appropriate safety testing approaches for nanomaterials
- integrating results from new "data-rich" techniques (e.g., genomics, high throughput screening) with traditional toxicology data to provide public health context
- providing guidance for the proper use of new types of information in hazard identification and characterization

Other significant leadership changes at NIEHS/NTP include the appointments of Dr. Paul Foster to head the Toxicology Branch and Dr. Raymond Tice to head the Biomolecular Screening Branch (BSB).

Communication and Public Outreach

Maintaining open communications and ensuring dialogue with federal and state agencies, industry, nongovernment groups, academia, and the public are goals of the NTP. NTP advisory groups (see page 7) provide regular scientific and public peer review and input. NTP conferences and workshops remain a priority and are designed to bring researchers, regulators, policy makers, and the public together to examine issues and achieve consensus on future directions in toxicology and risk assessment.

Distribution of NTP study results, program plans, initiatives, announcements, press advisories, and publications is accomplished in several ways to communicate as much as possible with the public. Information is routinely distributed to interested parties through *Federal Register* announcements on the NTP website (*http://ntp.niehs.nih.gov*). The website offers access to information about the program that details and highlights ongoing and future initiatives, announcements, NTP centers, NTP publications, and study data. The public can subscribe to the NTP ListServ on the website to receive news and updates. Currently the ListServ has more than 4,000 subscribers. The NTP publishes the quarterly newsletter, *NTP Update*, which can be downloaded from the NTP website. NTP actively participates in the annual Society of Toxicology (SOT) meeting. At the 2009 SOT meeting in Baltimore, Maryland, NTP staff participated in eight platform sessions, one workshop session, two symposia, one featured session, the SOT/Eurotox debate, and more than 60 posters.

The NIEHS/NTP Central Data Management Office oversees distribution (upon request) of specific chemical study information and printed NTP documents – NTP study status reports, final and draft copies of NTP Technical Report Series, and background documents for substances nominated to the NTP. On-line, searchable access is available for the Report on Carcinogens (*http://ehponline.org*) and the NTP Technical, Toxicity, and Genetically Modified Models series reports (*http://ntp.niehs.nih.gov* or *http://ehp.niehs.nih.gov/ntp/docs/ntp.html*).

The NTP is interested in and welcomes stakeholder input into its programs and priorities. Nominations, inquiries, and comments from the public and other interested parties are encouraged at any time. The NTP Office of Liaison, Policy and Review at the NIEHS under the direction of Dr. Mary S. Wolfe serves as the focal point for receiving input to the program and for overseeing the distribution of information about programs, workshops, initiatives, and other NTP projects.

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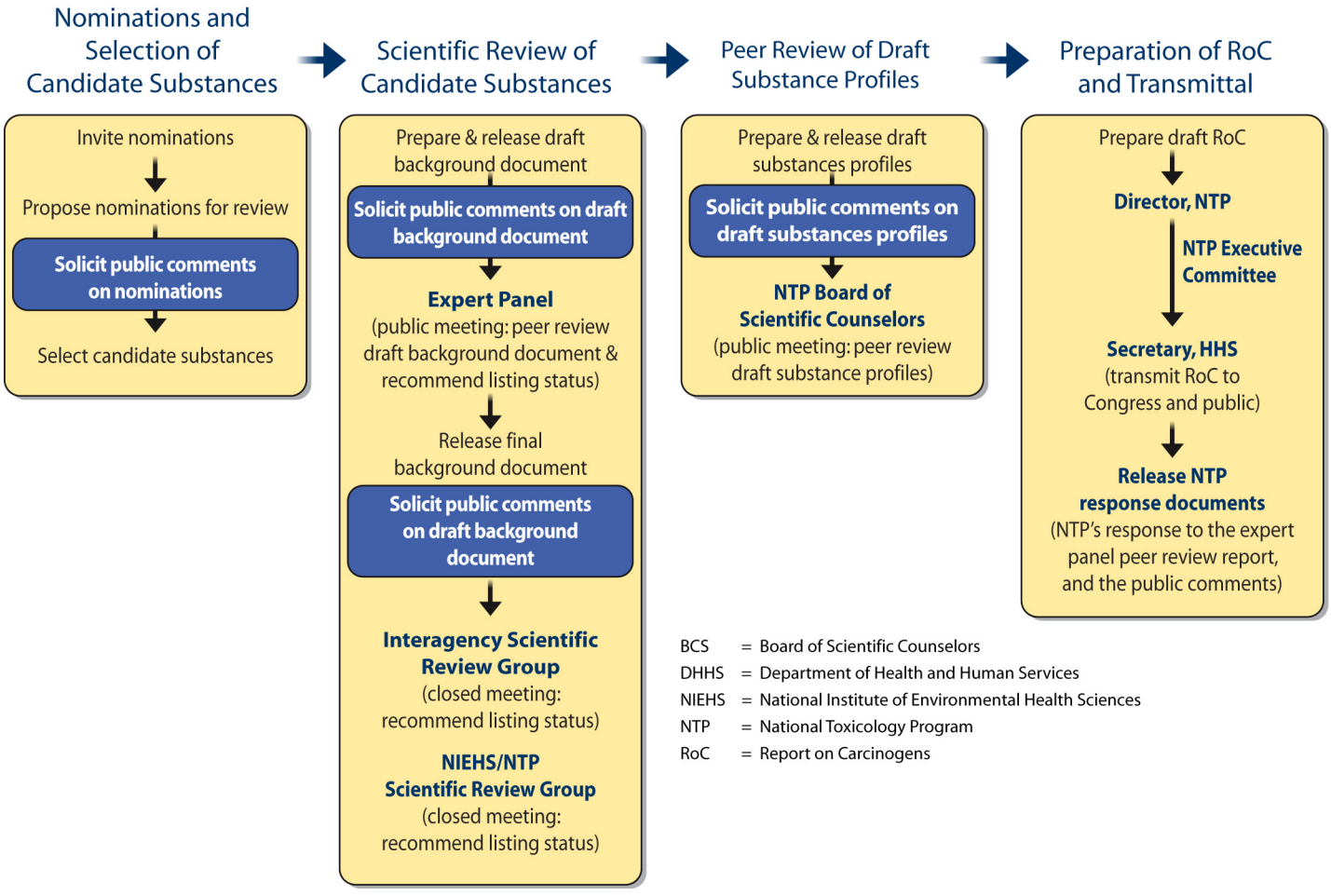
Report on Carcinogens

The Report on Carcinogens (RoC) is a congressionally mandated listing [Section 301(b)(4) of the Public Health Services Act, 42 U.S.C. 241(b)(4)] of substances (1) that either are *known to be human carcinogens* or *may reasonably be anticipated to be human carcinogens* and (2) to which a significant number of persons residing in the United States are exposed. The Secretary of Health and Human Services has delegated preparation of the RoC to the NTP, with assistance from other Federal health and regulatory agencies.

The RoC is an informational, scientific, and public health document that identifies and discusses agents, substances, mixtures, or exposure circumstances ("substances") that may pose a carcinogenic hazard to human health. It serves as a meaningful and useful compilation of data for listed substances on (1) the carcinogenicity, genotoxicity, and biological mechanisms in humans and/or animals, (2) the potential for exposure, and (3) any relevant regulations promulgated by Federal agencies. Dr. Ruth Lunn is the Director of the RoC Center. SRA International, Inc., provided contract support for preparation of the RoC in FY 2009.

Figure 3: NTP Report on Carcinogens Review Process



The process for preparing the 12th RoC, released on April 16, 2007, was designed to enhance the scientific development of the report and address guidance from the Office of Management and Budget Information Quality Bulletin for Peer Review. Information about this process can be found at *http://ntp.niehs.nih.gov/go/15208*. Two important new elements in the 12th RoC review process are public peer review of (1) draft background documents by ad hoc scientific expert panels and (2) draft substance profiles by the NTP BSC.

Reviewing nominations to the RoC is a multi-step, formal, and open process, as shown in Figure 3. The nomination of substances for listing in or removal from the RoC is open to all interested individuals and groups. The RoC Center prepares a draft background document on each substance under review that is peer-reviewed by an external scientific *ad hoc* panel at a public meeting. Three independent scientific groups make independent recommendations to the NTP on the listing status of candidate substances. Taking into account recommendations from the three review groups and the public comments, the NTP drafts a substance profile, which contains its preliminary listing status recommendation, the science that supports the recommendation, and information on use, production, exposure, and current regulations. The NTP BSC meets publicly to peer review the draft substance profile. Public comments are solicited several times during the review process and are provided to each review group as available. The NTP prepares the draft RoC (which contains substance profiles for newly proposed and listed substances and substances listed in previous editions of the RoC) for review and comment by the NTP Executive Committee. The NTP Director receives the input from all reviews plus the public comments and submits the final draft RoC to the Secretary, DHHS, for review and approval.

Scientific review of nominations to the 12th edition of the RoC continued through FY 2009. Candidate substances for the 12th RoC are listed in Table 5. The RoC Center convened an expert panel to review the draft background document for cobalt-tungsten carbide: powders and hard metals on December 9-10, 2008, in Chapel Hill, NC. The expert panel peer reviewed the draft background document and made a recommendation to list cobalt-tungsten carbide: powders and hard metals as reasonably anticipated to be a *human carcinogen* based on limited evidence of carcinogenicity in humans and supporting mechanistic data.

The RoC Center convened a second expert panel in FY 2009 on June 9-10, 2009, in Chapel Hill, NC, to review the draft background document and consider a recommendation for glass wool fibers. This was in response to a recommendation by the North American Insulation Manufacturers Association to change the listing status for glass wool fibers in the 11th RoC, which currently lists glass wool of respirable size as *reasonably anticipated to be a human carcinogen*. The expert panel recommended that a distinct class of glass wool fibers (longer, thinner and less soluble) be classified as reasonably anticipated to be a human carcinogen in the 12th RoC. The panel recommended that types of glass wool fibers that are not in this class should not be classified either as known to be a human carcinogen or as reasonably anticipated to be a human carcinogen and should be removed from the RoC listing.

Table 5: Candidate Substances for the 12th Report on Carcinogens (as of December 2009)

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Aristolochic Acids NIEHS	The principle extract from *Aristolochia*; a mixture of nitrophenanthrene carboxylic acids; used in traditional Chinese medicine as anti-rheumatics, as diuretics, in the treatment of edema, and for other conditions such as hemorrhoids, coughs and asthma.	IARC finding of sufficient evidence of carcinogenicity in animals and limited evidence in humans. (IARC Monograph Vol. 82, 2002).
Captafol [2425-06-01] NIEHS	A fungicide that has been widely used since 1961 for the control of fungal diseases in fruits, vegetables, and some other plants. Use of captafol in the United States was banned in 1999.	IARC finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 53, 1991). IARC also noted that captafol gives positive results in many genetic assays, including the *in vivo* assay for dominant lethal mutation.
Cobalt–Tungsten Carbide: Powders Hard Metals NIEHS	Composites of carbides with a metallic cobalt, used to make cutting and grinding tools, dies, and wear products for a broad spectrum of industries, including mining and oil and gas drilling.	Recent human cancer studies on the hard metal manufacturing industry showing an association between exposure to hard metals (cobalt tungsten-carbide) and lung cancer.

Candidate Substance [CASRN] Nominator	Primary Uses/Exposures	Basis of Nomination
Formaldehyde [50-00-0] NIEHS – for reclassification	Primarily used to produce resins for the production of many different products, including plastics, adhesives and binders for wood products, pulp and paper, and synthetic fibers, and in textile finishing. It is also used as a disinfectant and preservative and as an intermediate for many industrial chemicals.	Nominated for reconsideration based on the 2004 IARC review, which concluded that there was sufficient evidence for the carcinogenicity of formaldehyde in humans (IARC Monograph Vol. 88, 2004).
Glass Wool Fibers North American Insulation Manufacturers Association nominated glass wool (respirable size) for delisting	Glass wool fibers, which are a type of synthetic vitreous fibers, are an inorganic fibrous material manufactured primarily from glass and processed inorganic oxides. The major uses of glass wool are in thermal, electrical, and acoustical insulation, weatherproofing, and filtration media. Some special-purpose glass wool fibers are used for high-efficiency air filtration media and acid battery separators.	Insulation glass wool: IARC finding of limited evidence of carcinogenicity in animals and evaluation as not classifiable as to its carcinogenicity to humans (Group 3; IARC Monograph Vol. 81, 2002). Special-purpose glass fibers: IARC finding of sufficient evidence of carcinogenicity in animals (IARC Monograph Vol. 81, 2002).
ortho-Nitrotoluene [88-72-2] NIEHS	Used to synthesize agricultural and rubber chemicals, azo and sulfur dyes, and dyes for cotton, wool, silk, leather, and paper.	Results of an NTP bioassay (NTP Technical Report 504, 2002), which reported *clear evidence of carcinogenic activity* in rats and mice.
Riddelliine [2346-96-0] NIEHS	Found in a class of plants growing in the western United States. Cattle, horses, and sheep ingest these toxic plants. Residues have been found in milk and honey.	Results of an NTP bioassay (NTP Technical Report 508, 2003), which reported *clear evidence of carcinogenic activity* in male and female rats and mice.
Styrene [100-42-5] Private Individual	Used in the production of polystyrene, acrylonitrile-butadiene-styrene resins, styrene-butadiene rubbers and latexes, and unsaturated polystyrene resins.	IARC finding of limited evidence of carcinogenicity in animals and limited evidence of carcinogenicity in humans (IARC Monograph Vol. 82, 2002).

International Agency for Research on Cancer (IARC). IARC Monographs are available from *http://monographs.iarc.fr/.*
NTP Technical Reports are available at *http://ntp.niehs.nih.gov/* see "NTP Study Reports."

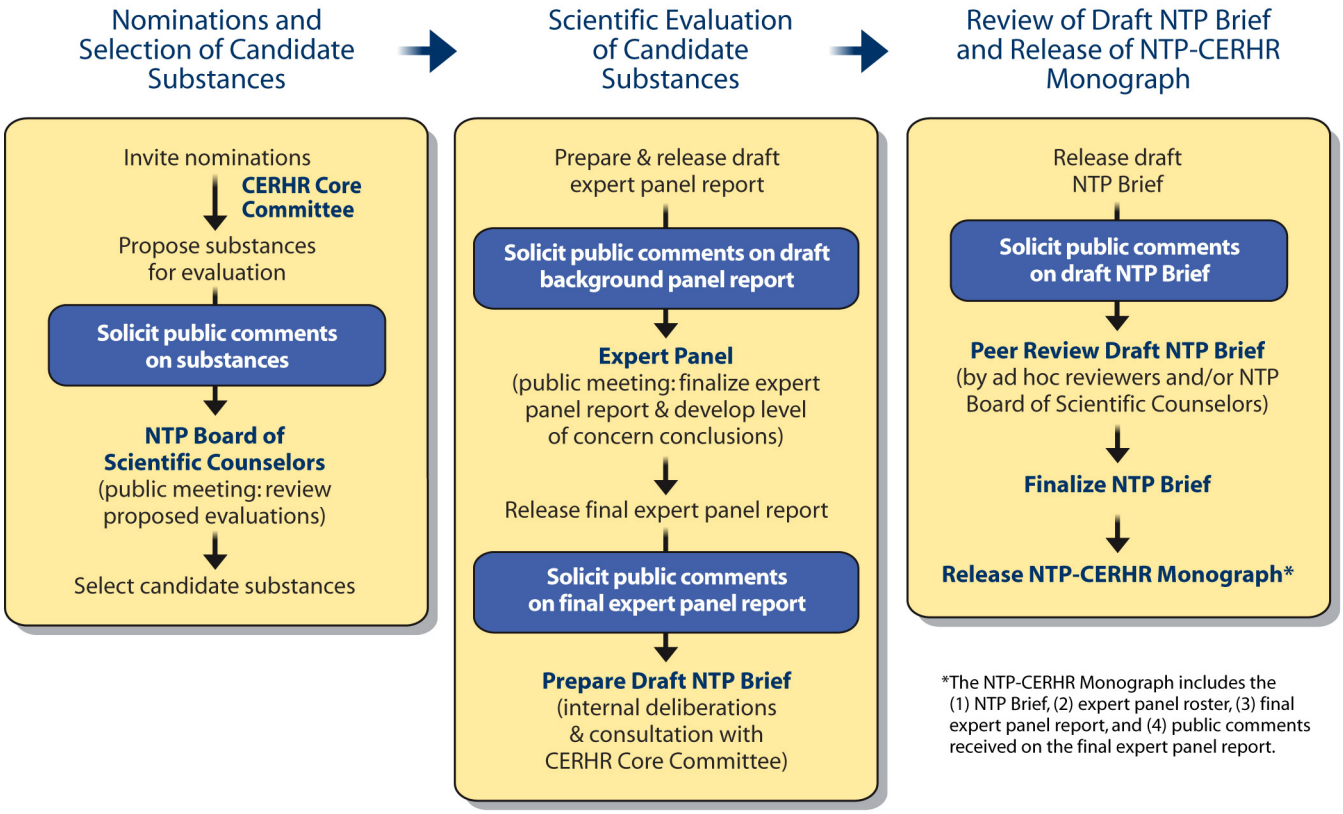
Contact Information: Report on Carcinogen Center, Dr. Ruth Lunn, *lunn@niehs.nih.gov.*
RoC website: *http://ntp.niehs.nih.gov* select "Report on Carcinogens."

Center For the Evaluation of Risks to Human Reproduction

The Center for the Evaluation of Risks to Human Reproduction (CERHR) was established in 1998 to serve as an environmental health resource to the public and regulatory and health agencies. CERHR is located at the NIEHS, and Dr. Kristina Thayer served as Acting Director in FY 2009. CERHR publishes monographs that assess the potential for substances to cause adverse effects on reproduction and development in humans.

CERHR follows a formal process (Figure 4) for nomination, selection, and evaluation of substances that includes evaluation by an *ad hoc* panel of scientists with topic-specific expertise and three formal solicitations of public comment. CERHR selects substances for evaluation based on several factors, including production volume, extent of human exposures, public concern about the chemical hazard, and the extent of published data from studies of reproductive or developmental toxicity. The NTP BSC (page 7) provides oversight for CERHR and offers advice on priorities, directions, and the adequacy of the CERHR process. The Core Committee is an advisory body consisting of scientists from government agencies on the NTP Executive Committee.

Figure4. Center for the Evaluation of Risks to Human Reproduction (CERHR) Evaluation Process



*The NTP-CERHR Monograph includes the (1) NTP Brief, (2) expert panel roster, (3) final expert panel report, and (4) public comments received on the final expert panel report.

CERHR convenes an expert panel whose meetings are open to the public. After an expert panel report is completed and public comments on the report are received, CERHR prepares a draft NTP Brief, in which the NTP considers all public comments and any additional scientific information that becomes available after the expert panel's deliberations and report are complete. The NTP Brief provides, in plain language, background information on the chemical, the findings of the expert panel report, discussion of any relevant data received after the expert panel meeting, and the NTP's conclusions on the potential for the chemical to cause adverse reproductive and/or developmental effects in exposed humans. Each NTP-CERHR monograph includes the expert panel's report, the NTP Brief, and any public comments received on the expert panel report. In the monograph, the NTP reaches conclusions regarding the possible effects of exposure of the substance on human reproduction or development. The possible levels of concern, from lowest to highest, are *negligible concern, minimal concern, some concern, concern,* and *serious concern*. Additional details about the CERHR process, CERHR expert panel evaluations, and monographs are available at the CERHR website (*http://cerhr.niehs.nih.gov*). The CERHR website also contains information covering common questions and concerns regarding a healthy pregnancy and the potential of various exposures to adversely affect fertility or the development of children.

CERHR focused on an evaluation of soy infant formula in FY 2009. Soy formula is fed to infants as a supplement or replacement for human milk or cow milk. Soy formula contains isoflavones such as genistein, daidzein, and glycitein, which are non-steroidal, estrogenic compounds that occur naturally in some plants and are often referred to as "phytoestrogens." In 2006, CERHR began evaluations of genistein and soy formula. An expert panel meeting was held in 2006, and the final expert panel reports for both substances were released in 2006. Draft NTP Briefs, which provided the NTP's conclusions regarding the potential for genistein or soy formula to adversely affect reproduction and/or development in exposed humans, were released for public comment and peer review in November 2006. CERHR did not finalize these evaluations, or issue the NTP-CERHR monographs on these substances. Since 2006, a substantial number of new studies related to human exposure or reproductive or developmental toxicity were published, and CERHR determined that an updated evaluation of soy infant formula was warranted. CERHR updated the initial draft report and released it for public comment. A public meeting of the expert panel was planned for December 2009. The panel will review and revise the draft expert panel report and reach conclusions regarding whether exposure to soy infant formula is a hazard to human development. The expert panel will also identify data gaps and research needs.

In October 2008 CERHR published the NTP Monograph on the Potential Human Reproductive and Developmental Effects of Hydroxyurea. The monograph presented NTP's conclusions:

- The NTP expresses *serious concern* that exposure of men to therapeutic doses of hydroxyurea may adversely affect sperm production. This level of concern is for all males who have reached puberty.
- The NTP concurs with the CERHR Expert Panel on Hydroxyurea that there is *concern* that exposure of pregnant women to hydroxyurea may result in birth defects, abnormalities of fetal growth, or abnormal postnatal development in offspring.
- The NTP concurs with the Expert Panel that there is *minimal concern* that exposure of children to therapeutic doses of hydroxyurea at 5–15 years of age will adversely affect growth.

Contact Information: Center for the Evaluation of Risks to Human Reproduction, Dr. Kristina Thayer, Acting Director, *thayer@niehs.nih.gov.* CERHR website: *http://cerhr.niehs.nih.gov*

NTP Interagency Center for the Evaluation of Alternative Toxicological Methods

The development, validation, acceptance, and harmonization of new, revised, and alternative toxicological test methods are coordinated in the Federal government through ICCVAM. NIEHS established ICCVAM in 1997 to implement a directive in the 1993 NIH Revitalization Act to develop a process to achieve the regulatory acceptance of scientifically valid alternative testing methods. Alternative methods are those methods that reduce, refine, or replace the use of animals. NICEATM was established in 1998 to administer ICCVAM, provide scientific support for ICCVAM activities, and conduct independent validation studies on promising test methods. The ICCVAM Authorization Act of 2000 (42 U.S.C. 285l-3) established ICCVAM as a permanent interagency committee under NICEATM, and specified the purposes and duties of the committee. Dr. William Stokes (Rear Admiral, U.S. Public Health Service) is the NICEATM Director and Executive Director of the ICCVAM. Integrated Laboratory Systems, Inc., provided contract support for NICEATM in FY 2009.

ICCVAM and NICEATM work to promote the validation and regulatory acceptance of new, revised, and alternative toxicological test methods that are more predictive of human and ecological effects than those currently available and that refine, reduce, and replace animal use whenever possible. The desired outcomes from these new methods are to improve agencies' abilities to assess risk and make regulatory decisions, promote more humane animal use, and reduce and replace animal use. NICEATM, in conjunction with ICCVAM, convenes scientific peer review panels to evaluate the validation status of proposed alternative testing methods for which validation studies have been completed to assess their accuracy and reproducibility across multiple labs. ICCVAM then develops formal test method recommendations for acceptance consideration by agencies, and proposes recommended test methods for adoption by international organizations. NICEATM and ICCVAM also convene workshops and expert panels to evaluate the adequacy of existing methods, identify promising test methods for further development and validation, evaluate the interim validation status of methods, and evaluate proposed validation studies.

NICEATM receives test method nominations and submissions for ICCVAM to consider and review (see *http://iccvam.niehs.nih.gov*). Test methods can be nominated for validation studies or technical reviews. The ICCVAM evaluation process involves an initial assessment by NICEATM of the adequacy and completeness of the test method nomination or submission, and a determination by ICCVAM of the priority of the proposed method for technical evaluation or validation studies. Once a proposed test method is accepted for evaluation or validation, ICCVAM assembles an interagency working group with appropriate scientific and regulatory expertise to collaborate with NICEATM on the evaluation process. Depending on the validation status of the proposed test method, ICCVAM, in conjunction with NICEATM, develops recommendations and priorities for appropriate evaluation activities. Such efforts might include an expert workshop, an expert panel meeting, a peer review meeting, an expedited peer review process, or a validation study. Information on the status and results of NICEATM and ICCVAM activities, including meeting reports and background documents, is available on the NICEATM-ICCVAM website. ICCVAM has contributed to the approval or endorsement of 27 alternative safety-testing methods by Federal regulatory agencies since its establishment in 1997. Recent NICEATM publications, meetings, and test methods currently under review, and project status are presented in Tables 6, 7, 8, and 9, respectively.

Together with counterparts from Japan, Europe, and Canada, NICEATM was one of four validation centers that will cooperate as the result of a Memorandum of Cooperation (MOC) signed on April 27, 2009, establishing the International Cooperation on Alternative Test Methods (ICATM). The agreement promotes enhanced international cooperation and coordination of the scientific validation of alternative toxicity testing methods to reduce, refine, and/or replace animal use for regulatory testing. The MOC was signed by NIEHS and NTP Director Dr. Linda Birnbaum, for NICEATM and ICCVAM; Dr. Elke Anklam, Director of the Institute for Consumer Protection and

Health, for the European Centre for the Validation of Alternative Methods; Dr. David Blakey, for the Environmental Health Science and Research Bureau within Health Canada; and Dr. Masahiro Nishijima, Director General for the National Institute of Health Sciences, for the Japanese Center for the Validation of Alternative Methods. The goals of the ICATM framework are (1) to establish international cooperation in the critical areas of validation studies, independent peer review, and development of harmonized recommendations to ensure that alternative methods/strategies are more readily accepted worldwide and (2) to establish international cooperation necessary to ensure that new alternative test methods/strategies adopted for regulatory use will provide equivalent or improved protection for people, animals, and the environment, while replacing, reducing, or refining (causing less pain and distress) animal use whenever scientifically feasible. The ICATM framework has been endorsed by ICCVAM and adopted by the International Cooperation on Cosmetics Regulation.

NICEATM-ICCVAM participated in the 7th World Congress on Alternatives and Animal Use in the Life Sciences in August/September 2009. NICEATM-ICCVAM scientists presented eight posters highlighting their recent progress. One poster, titled *International Acceptance of* In Vitro *Alternative Ocular Safety Testing Methods: The Bovine Corneal Opacity and Permeability Test Method (Draft OECD TG 437)*, won an award presented by the Doerenkamp-Zbinden Foundation. The poster described the validation and international acceptance of the bovine corneal opacity and permeability test method to identify ocular corrosives and severe irritants.

On November 12, 2008, Dr. Stokes received the James A. McCallam Award at the 114th meeting of the Association of Military Surgeons of the United States. This award recognized Dr. Stokes' outstanding accomplishments in the field of medicine and health.

On December 17, 2008, the Humane Society of the United States and the Procter and Gamble Company awarded the North American Alternative Awards to the Tox21 program. Tox21 is led by Dr. Christopher Austin of the National Human Genome Research Institute, Dr. Robert Kavlock of the EPA, and Dr. Raymond Tice, Deputy Director of NICEATM from 2006 to 2008. The $25,000 award, which recognizes outstanding scientific contributions to the advancement of viable alternatives to animal testing, will support automated, robotic, high-volume *in vitro* studies of chemicals.

NICEATM-ICCVAM is planning two meetings for FY 2010:

- Independent peer review panel meeting: *Evaluation of an* In Vitro *Stably Transfected ER Transcriptional Activation Assay for Identification of Potential Endocrine Disruptor Activity*
- *International Workshop on Alternative Methods to Reduce, Refine, and Replace the Use of Animals in Vaccine Potency and Safety Testing: State of the Science and Future Directions*

Table 6: NICEATM-ICCVAM Publications in FY 2009

Date	Title
Oct 23, 2008	*Biennial Progress Report: Interagency Coordinating Committee on the Validation of Alternative Methods – 2006-2007*
Jan 1, 2009	*Recommended Performance Standards: Murine Local Lymph Node Assay*
Mar 1, 2009	*ICCVAM Test Method Evaluation Report - The Reduced Murine Local Lymph Node Assay: An Alternative Test Method Using Fewer Animals to Assess the Allergic Contact Dermatitis Potential of Chemicals and Products*
Mar 1, 2009	*Report on the ICCVAM-NICEATM/ECVAM/JaCVAM Scientific Workshop on Acute Chemical Safety Testing: Advancing In Vitro Approaches and Humane Endpoints for Systemic Toxicity Evaluations*
Jun 1, 2009	*Independent Scientific Peer Review Panel Report - Updated Validation Status of New Versions and Applications of the Murine Local Lymph Node Assay: A Test Method for Assessing the Allergic Contact Dermatitis Potential of Chemicals and Products*
Jul 13, 2009	*Independent Scientific Peer Review Panel Report: Evaluation of the Validation Status of Alternative Ocular Safety Testing Methods and Approaches*

Table 7: NICEATM-ICCVAM Workshops and Peer Review Meetings in FY 2009

Date	Meeting	Topics
Apr 28-29, 2009	Second Independent Scientific Peer Review Panel Meeting: Updated Evaluation of New Versions and Applications of the Murine Local Lymph Node Assay (LLNA).	• Application of the LLNA for evaluating pesticide formulations and other products • Three modified versions of the LLNA not requiring the use of radioactive markers: – LLNA: Daicel adenosine triphosphate (DA) – LLNA: bromodeoxyuridine (BrdU) detected by flow cytometry – LLNA: BrdU detected by enzyme-linked immunosorbent assay (ELISA)
May 19-21, 2009	Independent Scientific Peer Review Panel Meeting: Alternative Ocular Safety Testing Methods	• A proposal for the routine use of topical anesthetics, systemic analgesics, and humane endpoints to avoid and minimize pain and distress during *in vivo* ocular irritation testing • The validation status of four *in vitro* test methods for identifying moderate and mild irritants and substances not classified as ocular irritants • The validation status of the *in vivo* low volume eye test • The validation status of a testing strategy that proposes the use of three *in vitro* test methods to assess eye irritation potential of antimicrobial cleaning products

Table 8: Actions on Nominations or Submissions by NICEATM-ICCVAM in FY 2009

Test Method Nomination or Submission	Nominator or Sponsor/Activity Status
NTP two-year toxicology and carcinogenesis rodent studies	Anonymous/Low priority by SACATM and ICCVAM. Higher priority should be given to validation of non-animal test methods for carcinogenicity.
In vitro test method for assessment of the eye irritation potential of antimicrobial cleaning products	Alternatives Testing Steering Committee: JohnsonDiversey, S.C. Johnson and Son, Inc., The Procter and Gamble Company, and The Accord Group/under evaluation
Request for assessment of the validation of the LLNA for classification of sensitizers	Consumer Product Safety Commission/under evaluation

Table 9: NICEATM-ICCVAM Recommendations in FY 2009

Test Method	ICCVAM Recommendations/Agency Status
In Vitro Cytotoxicity Test Methods: 3T3 Cells	U.S. acceptance in 2008. Anticipated OECD acceptance in 2010.
In Vitro Cytotoxicity Test Methods: NHK Cells	U.S. acceptance in 2008. Anticipated OECD acceptance in 2010.
Acute Toxic Class Method (inhalation)	OECD Test Guideline 436 in 2009.
Fixed Dose Procedure (inhalation)	Anticipated OECD evaluation and acceptance in 2010.
Up-and-Down Procedure (dermal)	Data collection in progress. Anticipated evaluation in 2010.
LabCyte EPI-MODEL24 assay for dermal corrosivity	Anticipated OECD evaluation in 2010.
EpiDerm™, EpiSkin™, SkinEthic RHE, LabCyte EPI-MODEL24 for dermal irritation	Anticipated OECD evaluation in 2010.
Updated protocol for the murine LLNA	Anticipated U.S. Federal agency acceptance in 2010. OECD Test Guideline 429 updated; anticipated OECD acceptance in 2010.
Reduced LLNA; LLNA Performance Standards; Updated LLNA Test Method Protocol (20% animal reduction)	Anticipated U.S. Federal agency and OECD acceptance in 2010.
Nonradiolabeled LLNA methods (BrdU-ELISA and DA)	Evaluation in progress. Recommendations to U.S. Federal agency and acceptance new OECD test guideline anticipated in 2010.
Nonradiolabeled LLNA method (BrdU-Flow Cytometry)	Interlaboratory validation study required.

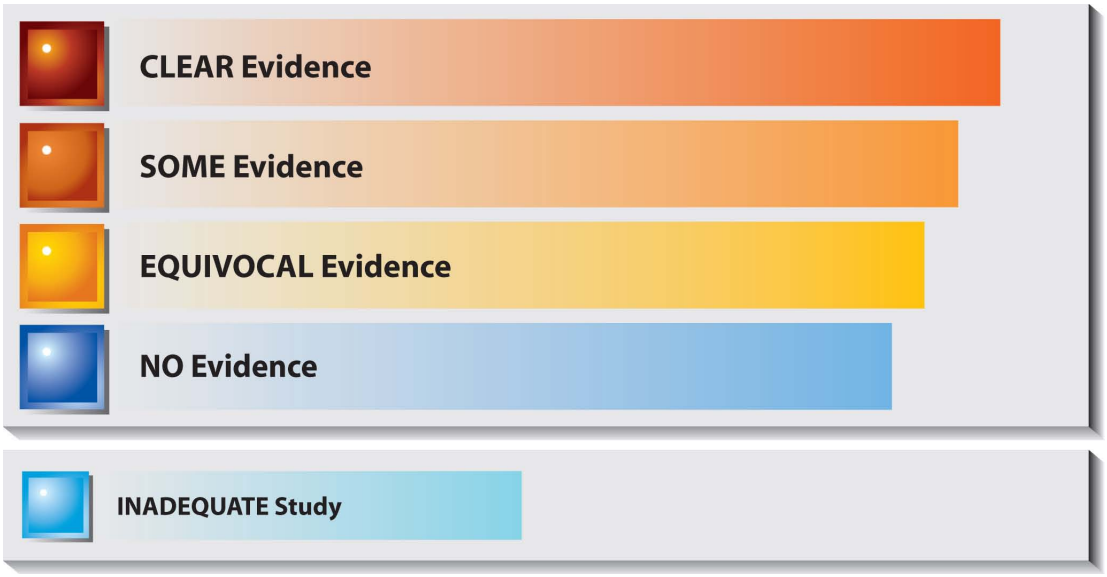
Test Method	ICCVAM Recommendations/Agency Status
Use of LLNA for skin sensitization potency categorization	Evaluation in progress. Recommendations anticipated in 2010.
Use of LLNA for testing mixtures, metals, and aqueous solutions	Evaluation in progress. Recommendations anticipated in 2010.
In Vitro Micronucleus Assay	OECD approval in 2009.
In Vivo Comet Assay	Validation studies in progress.
In Vitro Comet Assay	Planned after *in vivo* comet assay studies.
Cell Transformation Assays (pH 6.7, pH 7.0, Balb/c 3T3 cell)	ECVAM-led validation studies completed. Evaluation in progress.
BHAS Cell Transformation Assay	JaCVAM-led validation study in progress.
LUMICELL® ER TA Transcription Activation Assay	Validation studies in progress. Evaluation anticipated in 2010.
MCF-7 Cell Proliferation Assay	Validation studies in progress. Evaluation anticipated in 2011.
Five *in vitro* pyrogenicity test methods	ICCVAM recommended that although none of these test methods can be considered a complete replacement for the Rabbit Pyrogen Test (RPT) for detection of Gram-negative endotoxin, they can be considered for use to detect Gram-negative endotoxin in human parenteral drugs on a case-by-case basis, subject to validation for each specific product to demonstrate equivalence to the RPT, in accordance with applicable U.S. Federal regulations. When used in this manner, these methods should be able to reduce the number of animals used for pyrogenicity testing. All Federal agencies accepted or endorsed ICCVAM recommendations in 2009. European Pharmacopoeia accepted the methods in March 2009.
Bovine Corneal Opacity and Permeability (BCOP) and Isolated Chicken Eye (ICE) tests for ocular corrosivity/severe irritation	ICCVAM recommended that the BCOP and ICE test methods can be used in a tiered testing strategy to determine ocular hazards, with specific limitations for certain chemical classes and/or physical properties. The methods should always be considered before using animals for ocular testing and should be used where determined appropriate. These methods do not involve the use of live animals; tissues used are obtained from animals intended for food consumption. OECD Test Guidelines 437 and 438 for these methods were adopted in 2009.
Integrated non-animal testing strategy for eye irritation potential of antimicrobial cleaning products	Evaluation in progress. Recommendations to U.S. agencies and acceptance anticipated in 2010.
BCOP, ICE, Isolated Rabbit Eye and Hen's Egg Test/Choriallantoic Membrane for nonsevere ocular irritation and identification of substances that do not require labeling as ocular hazards	Evaluation in progress. Recommendations to U.S. agencies and acceptance anticipated in 2010.
Cytosensor Microphysiometer test method for nonsevere ocular irritation and identification of substances that do not require labeling as ocular hazards	Evaluation in progress. Recommendations to U.S. agencies and acceptance anticipated in 2010.
Routine use of topical anesthetics, systemic analgesics, and humane endpoints in *in vivo* ocular safety testing	Evaluation in progress. Recommendations to U.S. agencies and acceptance anticipated in 2010.
In vivo low-volume eye test	Evaluation in progress. Recommendations to U.S. agencies and acceptance anticipated in 2010.

Contact information: NTP Interagency Center for the Evaluation of Alternative Toxicological Methods, Dr. William Stokes, Director. *niceatm@niehs.nih.gov* or NICEATM/ICCVAM website *http://iccvam.niehs.nih.gov*

Highlighted Activities

Levels of Evidence Criteria for Immunotoxicology, Reproductive Toxicology, and Developmental Toxicology Studies

The NTP describes the results of individual toxicology and carcinogenicity studies on a substance and notes the strength of evidence for conclusions regarding each study (*http://ntp.niehs.nih.gov/go/baresults*). In 2008, the NTP began developing three sets of specific criteria to describe the conclusions from its immunotoxicology, reproductive toxicology, and developmental toxicology studies. The draft criteria were patterned after the carcinogenicity levels of evidence criteria used for the technical reports. The NTP convened working groups of the BSC in August and September 2008 to evaluate the utility and applicability of the three sets of draft criteria. The working group reports, including proposed revisions to the criteria, were presented to the BSC in November 2008; the reports were approved, and the BSC had additional discussion (*http://ntp.niehs.nih.gov/go/9741*). Using the input from the working groups and the BSC, and with endorsement by the NTP Executive Committee in December 2008, the NTP finalized the criteria and presented them at an exhibitor's session at the annual Society of Toxicology meeting in March 2009. The criteria are now in place and will be used for future immunotoxicology, reproductive toxicology, and developmental toxicology studies. The NTP is also considering undertaking a retrospective exercise using these criteria on conclusions from selected previous NTP reports to ensure consistency in criteria applications. It is anticipated that the criteria (available at *http://ntp.niehs.nih.gov/go/33690*) will clarify the official government opinion on the hazards posed by substances evaluated by the NTP, which will increase the usefulness of the non-cancer studies for regulatory agencies.



Contact Information: Dr. Paul Foster, *foster2@niehs.nih.gov* or Dr. Dori Germolec, *germolec@niehs.nih.gov*.

Cellular Phone Radiation Emissions

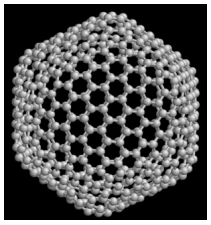
The NTP is conducting a multi-year study to address the potential health-related adverse effects of radiation emitted by cellular phones and cell towers. More than 270 million Americans use wireless communication devices; however, the potential health effects of long-term exposure to radiation emissions from these devices are unknown. The overall goal of the NTP's studies is to determine the potential toxic and/or carcinogenic effects of exposure to cellular phone radiofrequency emissions in laboratory animals. The animal studies are being conducted in three phases: (1) pilot studies to determine appropriate field strengths of emissions; (2) subchronic toxicology using exposures of up to two months; and (3) chronic toxicology and carcinogenicity studies. These NTP studies will provide information regarding the safety of exposure to radiofrequency radiation and strengthen the science base for determining any potential health effects in humans. These data could contribute to information used by the Federal government, including the FDA, in making decisions about radiofrequency radiation health issues to protect public health and safety.

The *Expert Conference on Cell Phones and Health: Science and Public Policy Questions* was held on September 14, 2009, in Washington, DC. Dr. Chris Portier, NIEHS Associate Director, served on the Steering Committee. Dr. Michael Wyde, NTP toxicologist, provided an update of the current animal research and described studies using reverberation chambers for the tests. The U.S. Senate then conducted a hearing on radiation emission safety. Dr. John Bucher, NTP Associate Director, presented testimony, stating, "While the current scientific evidence has not conclusively linked cell phone use with any health problems, we and other scientific organizations evaluating the available studies have concluded that better data are needed to establish any potential health risks from the low-level radiofrequency radiation exposures associated with their use."

Contact Information: Dr. Michael Wyde, *wyde@niehs.nih.gov*

Nanotechnology Safety Initiative

Nanoscale materials are materials that have at least one dimension in the size range of approximately 1-100 nm in size. While they are already appearing in commerce as industrial and consumer products and as novel drug delivery formulations, little research has focused on the potential toxicity of manufactured nanoscale materials. Also, the unique and diverse physicochemical properties of nanoscale materials suggest that their toxicological properties may differ from those of materials of similar composition but larger size.



Fullerene

The NTP is currently engaged in a broad-based research program to address potential human health hazards associated with the manufacture and use of nanoscale materials. This initiative is driven by the current and anticipated future focus on nanotechnology research and development. Ongoing research activities are initially focusing on several classes of materials, including nanoscale metal oxide powders (titanium dioxide and cerium oxide), cadmium-based fluorescent nanocrystalline semiconductors (quantum dots), carbon fullerenes, carbon nanotubes, and metal-based nanoparticles (nanosilver and nanogold).

The ultimate goal of this research program is to evaluate the toxicological properties of several nanoscale material classes that represent a cross section of composition, size, surface coatings, and physicochemical properties, and to use these properties to investigate fundamental questions concerning if and how nanoscale materials interact with biological systems and potentially cause adverse effects in humans.

In FY 2009 the NTP was invited to participate in a number of working and advisory groups:

- EPA Nanomaterial Case Studies Workshop, September 2009
- Nanotechnology Environmental and Health Implications Interagency Workgroup, May 2009
- Interagency Advisory Group for National Institute of Standards and Technology Activities on Nano-EHS Measurement and Standards, May 2009.

Drs. Nigel Walker and John Bucher published *A 21st century paradigm for evaluating the health hazards of nanoscale materials* in *Toxicological Sciences*. They suggested that diverse engineered nanomaterials offer a tailor-made test case for the potential use of new, high throughput, "predictive toxicity" strategies, such as envisioned in the 2007 National Research Council report *Toxicity Testing in the 21st Century*.

Titanium dioxide

Current NTP projects include evaluating the pharmacokinetics of nanoscale silver in rodents. The NTP has completed two subchronic 90-day inhalation studies of fullerene C60 (exposures to each of two particle sizes, 50 nm and 1 µm, each in both rats and mice via nose-only inhalation). The NTP has completed physicochemical characterization of 24 multi-walled nanotubes of varying sizes, lengths, and vendors. These data are being used to plan subchronic inhalation studies of selected multi-walled nanotubes. Dr. Walker gave seven invited presentations on nanomaterials in FY09.

Contact Information: Dr. Nigel Walker, *walker3@niehs.nih.gov.*

Mold Studies

Aspergillus mold

Natural disasters (e.g., hurricanes), new construction methods, and better sealing and insulation in buildings have all led to an increase in indoor mold levels. Exposure to elevated levels of indoor mold has been associated with respiratory, neurological, and gastrointestinal changes. NTP is designing studies to evaluate the health effects of the commonly found molds *Aspergillus*, *Penicillium*, and *Stachybotrys* to better understand how exposure to mold may cause disease.

Specific aims of the NTP studies are (1) to assess organ system toxicity following inhalation exposure to molds, (2) to evaluate the available biomarkers of exposure and effect (both general and specific for the organisms to be studied), and (3) to evaluate how different molds contribute to overall health effects by studying molds both as individual isolates and as mixtures. Two test mixtures that attempt to simulate real-life exposure scenarios (one from a water-damaged building in New Orleans and the other from a building with reported "sick building syndrome") will be used in subchronic inhalation studies in rodents.

Contact Information: Dr. Dori Germolec, *germolec@niehs.nih.gov.*

Herbal Medicines and Dietary Supplements

Herbal and dietary supplements are a major focus area for the NTP. The NTP is currently studying many of the 25 top-selling herbal and dietary supplements. Table 10 lists the substances for which studies are completed, ongoing, or planned. The substances can be loosely classified as "women's health" (black cohosh, gum guggul, dong quai), "cancer chemopreventives" (e.g., green tea extract, indole carbinol, resveratrol, melatonin), "anti-aging" (e.g., ginseng, glucosamine/chondroitin sulfate, *Ginkgo biloba*, vincamine), weight loss/sports aids (e.g., *Usnea* lichen/usinic acid, chitosan, *Garcinia cambogia*, bitter orange extract), and "multipurpose" (e.g., *Aloe vera*, *Echinacea*, kava, milk thistle, pulegone/pennyroyal, and senna laxative).

Table 10: Herbal Ingredients and Dietary Supplements

Substance [CASRN]	Project Leader	Use and/or Rationale
Aloe vera (oral) [8001-97-6]	Boudreau	Humans have widespread oral and dermal exposure to *Aloe vera* which lacks adequate toxicity information; there is a suspicion of carcinogenicity. The 1998 FDA Special Nutritional Adverse Event Monitoring System lists *Aloe vera* exposure as associated with numerous adverse effects in humans.
Arbutin [497-76-7]	Chan	Consumer exposure occurs through food, cosmetics, and dietary supplements. There is a lack of adequate toxicological data and suspicion of toxicity based on chemical structure.
Bitter orange extract	Hansen	Consumer exposure is through increasing dietary supplement use (it is the most common replacement for ephedra, banned from use by the FDA in 2003, in dietary supplements for weight loss). There is suspicion of toxicity and a lack of adequate toxicity data.
Chitosan [9012-76-4]	Chhabra	Chitosan is a popular dietary supplement used for weight loss. Several subacute studies in animals show that it has hypercholesterolemic properties and may influence weight gain; it may also cause vitamin and mineral deficiencies. There is a potential for vitamin E depletion and osteoporosis from ingestion.
Chondroitin sulfate/ Glucosamine [9007-28-7]	Leakey	Chondroitin sulfate is a dietary supplement widely used alone and in combination with glucosamine to alleviate pain and inflammation from osteoarthritis. No data are available on the possible adverse or toxic effects from long-term exposure.
Dong quai *(Angelica sinensis root)* and extract	Wyde	Dong quai has widespread use as a dietary supplement and in Chinese herbal medicine as an antispasmodic or blood purifier and for reducing pain, dilating blood vessels, and stimulation, as well as for relaxing uterine muscles. There is suspicion of toxicity based on estrogenic activity and chemical structure, and there is a lack of adequate toxicity data.
Echinacea purpurea, extract [90028-20-9]	Irwin	Echinacea is the most popular herbal supplement in the United States, creating widespread human exposure. It is used to stimulate the immune system, and there is a lack of scientific literature supporting its safety or efficacy.
Epigallocatechin (Green tea extract) [989-51-5]	Chan	Epigallocatechin is a potential cancer chemopreventive agent. It is an antioxidant thought to prevent tumorigenesis by protecting cellular components from oxidative damage via free radical scavenging. It is a major component of the polyphenolic fraction of green tea. It requires evaluation regarding its toxicity.
Garcinia cambogia extract [90045-23-1]	Wyde	*Garcinia cambogia* is marketed as an ephedra-free diet aid. There is consumer exposure through increasing dietary supplement use and a lack of adequate toxicity data.

Substance [CASRN]	Project Leader	Use and/or Rationale
Ginkgo biloba extract [90045-36-3]	Chan	There is potential for widespread exposure through use as a dietary supplement for "improving brain functioning" or "promoting radical scavenging activity." *Ginkgo biloba* clearly demonstrates biological activity and may be consumed in rather large doses for an extended period of time. Some ingredients are known mutagens or suspected carcinogens.
Ginseng [50647-08-0]	Chan	Ginseng has widespread use as a dietary supplement. There is a possibility that ginseng and ginsenosides may have anticarcinogenic activity, and a lack of toxicity information.
Glucosamine [3416-24-8]	Leakey	Glucosamine is a widely used dietary supplement, both alone and in combination with chondroitin sulfate, to alleviate pain and inflammation from osteoarthritis. There are no data on the possible adverse or toxic effects from long-term exposure.
Gum guggul extract	Wyde	Gum guggul has expanding use as a dietary supplement and has demonstrated biological effects on lipid metabolism, thyroid hormone homeostasis, female reproductive tissues, and endogenous nuclear hormone receptors, as well as the potential for serious drug interactions. There is a lack of available information to adequately assess safe use in humans.
Indole-3-carbinol [700-06-1]	Wyde	Indole-3-carbinol is marketed as a dietary supplement with projected rapid growth in sales. It is found in cruciferous vegetables and is under review at NCI as a chemopreventive agent for breast cancer. Substantial evidence exists that indole-3-carbinol can reduce the risk of cancers induced by several carcinogens when administered to animals.
Kava kava extract [9000-3-8]	Chan	Kava kava is a dietary supplement with widespread use. It has also been promoted as a substitute for Ritalin (methylphenidate) in children. Insufficient toxicity data are available. NCI recommended testing kava extract standardized to 30% kavalactones.
Melatonin [73-31-4]	Travlos	Melatonin, a hormone produced by the pineal gland, has become very popular as an over-the-counter hormone supplement as well as being used as a chemotherapeutic agent in cancer. There is a lack of toxicity information and a suggestion that melatonin may have the potential to cause ocular toxicity.
Milk thistle extract [84604-20-6] Silymarin [65666-07-1] Silybin [22888-70-6]	Dunnick	Milk thistle extract is a popular dietary supplement thought to have beneficial effects on the liver; however, there is limited information on its safety. Metabolism studies are needed to resolve questions regarding bioavailability of orally administered milk thistle extract. Milk thistle fruits contain silymarin, the active flavonoid constituent; one of silymarin's principal components is silybin.
Pulegone (Pennyroyal) [89-82-7]	Chan	The nomination of pulegone and menthofuran for testing is based on the potential for human exposure and the absence of carcinogenicity data. Pulegone is a major constituent of pennyroyal, and menthofuran is one of the metabolites of pulegone.
trans-Resveratrol [501-36-0]	Germolec	*trans*-Resveratrol is found in grapes and wine and is currently marketed in pure or extract form as a dietary supplement. It has numerous reported beneficial effects but toxicity is poorly characterized.
Retinyl palmitate	Howard	Retinyl palmitate was nominated for phototoxicity and photocarcinogenicity testing based on the increasing widespread use of this compound in cosmetic retail products for sun-exposed skin. There is a need to investigate the biochemical and histological changes in skin caused by retinyl palmitate and the association between topical application of retinoids and enhancement of photocarcinogenesis.
Senna (powdered) [8013-11-4]	Dunnick	The safety of laxatives is currently being reassessed by the FDA as a result of the testing of phenolphthalein for carcinogenicity in rodents. Senna has been reported as positive in the Ames test and a preliminary 2-year rat study showed an increase in lymph node hyperplasia. The Center for Drug Evaluation and Research is requesting a p53 hemizygous study to complement a 2-year rat study sponsored by the manufacturer.

Substance [CASRN]	Project Leader	Use and/or Rationale
α/ß Thujone mixture [546-80-5] [471-15-8]	Hooth	Thujone was identified through a review of direct food additives given "generally recognized as safe" status by the FDA. It has known toxicity that has caused it to be banned from some products. Twenty-four direct food additives in the FDA Priority-Based Assessment of Food Additives contain thujone. There is a potential for widespread consumer and worker exposure.
Usnea barbata, extract [84696-53-7]	Leakey	*Usnea barbata* is used as a dietary supplement for weight loss. Insufficient toxicity data are available.
Usnic acid and *Usnea* herb [125-46-2]	Leakey	Usnic acid and Usnea herb have widespread use in dietary supplements and personal care products. Adequate toxicological data are lacking, and there are numerous human adverse event reports.
Vincamine [1617-90-9]	Chan	Consumer exposure to vincamine occurs through dietary supplement use. There is a suspicion of toxicity and a lack of adequate toxicological data.

[1]*Testing Status and study results for completed studies can be found at http://ntp.niehs.nih.gov/ select "Testing Status of Agents at NTP" and "Study Results and Research Projects."*

Use of NTP Products by Other Agencies

Federal and state regulatory agencies use NTP study data and recommendations in considering the need to regulate and test specific chemicals to protect human health. Table 11 lists the NTP data and recommendations used in FY 2009.

Table 11: Federal and State Regulatory Agencies Use of NTP Study Data or Recommendations in FY 2009

Agency, Title, Additional Information	NTP Information Cited
ATSDR *Draft Toxicological Profile for Perfluoroalkyls* 74 FR 36492	NTP together with ATSDR and EPA identified categories of possible data needs addressed in the draft profile. The NTP's carcinogenicity study of perfluorooctanoic acid is mentioned in the section on ongoing studies.
California Office of Environmental Health Hazard Assessment (OEHHA) *Chemical Meeting on the Criteria for Listing via the Authoritative Bodies Mechanism: Methanol* Proposition 65	NTP-CERHR Monograph on the Potential Human Reproductive and Developmental Effects of Methanol (2003).
OEHHA *Notice of Intent to List 4-Methylimidazole* Proposition 65	TR-535 – Toxicology and Carcinogenesis Studies of 4-Methylimidazole in F344/N Rats and B6C3F1 Mice (feed studies) (2007).
OEHHA *Public Health Goals for Lead, Oxamyl, and Pentachlorophenol In Drinking Water*	(1) 11th RoC, Lead and lead compounds (2005). (2) TR-349 –Toxicology and Carcinogenesis Studies of Two Pentachlorophenol Technical-Grade Mixtures in B6C3F1 Mice (1989). (3) TR-483 –Toxicology and Carcinogenesis Studies of Pentachlorophenol in F344/N Rats (1999).
OEHHA *Technical Support Document on Proposed Public Health Goals for Trihalomethanes in Drinking Water*	(1) TR-282 – Toxicology and Carcinogenesis Studies of Chlorodibromomethane in F344/N Rats and B6C3F1 Mice (Gavage Studies) (1985). (2) TR-321 – Toxicology and Carcinogenesis Studies of Bromodichloromethane in F344/N Rats and B6C3F1 Mice (Gavage Studies) (1987). (3) NTP-89-018 – Chloroform Reproduction and Fertility Assessment in CD-1 Mice When Administered by Gavage, Report by Environmental Health Research and Testing, Inc., NTIS PB89-148639, (1988). (4) TR-350 – Toxicology and Carcinogenesis Studies of Tribromomethane) (Bromoform) in F344/N Rats and B6C3F1 Mice (Gavage Studies) (1989). (5) NTP-89-068 – Bromoform: Reproduction and Fertility Assessment in Swiss CD-1 Mice When Administered by Gavage (1989). (6) TR-426 – Comparative Toxicology Studies of Corn Oil, Safflower Oil, and Tricaprylin in Male F344/N Rats as Vehicles for Gavage (1994). (7) NTIS/PB97-111728 – Final Report on the Short-Term Reproductive and Developmental Toxicity of Chlorodibromomethane Administered in Drinking Water to Sprague Dawley Rats (1996). (8) NTIS/PB99-111262 – Final Report on the Short-Term Reproductive and Developmental Toxicity of Bromodichloromethane Administered in Drinking Water to Sprague Dawley Rats (1998). (9) 11th RoC (2005), Bromodichloromethane and Chloroform.

Agency, Title, Additional Information	NTP Information Cited
OEHHA *Final Public Health Goal for Trichloroethylene in Drinking Water*	(1) TR-83-1799 – Carcinogenesis Studies of Trichloroethylene (without Epichlorohydrin) in F344/N Rats and B6C3Fl Mice (Gavage Studies) (1983). (2) TR-273 – Toxicology and Carcinogenesis Studies of Trichloroethylene in Four Strains of Rats (ACI, August, Marshall, Osborne-Mendel) (Gavage Studies) (1988). (3) TR-243 – Carcinogenesis Studies of Trichloroethylene (without Epichlorohydrin) in F344/N Rats and B6C3F1 Mice (Gavage Studies) (1990). (4) IMM-96007 – Time Course Autoimmunity Study of Trichloroethylene in Female Brown Norway Rats (1997).
OEHHA *Proposed Public Health Goal for Antimony in Drinking Water*	TOX-11 – Toxicity Studies of Antimony Potassium Tartrate in F344/N Rats and B6C3F1 Mice (Drinking Water and Intraperitoneal Injection Studies) (1992).
OEHHA *Final Public Health Goal for 1,2,3-Trichloropropane In Drinking Water*	(1) TR-206 – Carcinogenesis Bioassay of 1,2-Dibromo-3-chloropropane in F344/N Rats and B6C3F1 Mice (Inhalation Studies) (1982). (2) TR-384 – Toxicology and Carcinogenesis of 1,2,3-Trichloropropane in F344/N Rats and B6C3F1 Mice (Gavage Studies) (1993). (3) 11th RoC (2005), Trichloropropane.
OEHHA *Pubic Health Goal for Hexavalent Chromium*	TR-546 – NTP Toxicology and Carcinogenesis Studies of Sodium Dichromate Dihydrate in F344/N Rats and B6C3F1 Mice (2008).
U. S. EPA *Regulation of Fuels and Fuel Additives: Changes to Renewable Fuel Standard Program* 74 FR 25053	11th RoC (2005), Acetaldehyde, Benzene, 1,3-Butadiene, Alcoholic beverages, Naphthalene.
U.S. EPA *Control of Emissions from Nonroad Spark-Ignition Engines and Equipment*	11th RoC (2005), Benzene, 1,3-Butadiene, Acetaldehyde, Naphthalene.
U. S. EPA *National Ambient Air Quality Standards for Lead*	11th RoC (2005), Lead and lead compounds.
U. S. EPA *Inert Ingredient: Exemption from the Requirement of a Tolerance for (S,S)Ethylenediaminedisuccinic Acid ((S,S)EDDS)*	TR-011 – Bioassay of Trisodium Ethylenediaminetetraacetate Trihydrate (EDTA) (1997). No carcinogenicity studies are available on (S,S)EDDS, but because of its similarity with EDTA, which shows no carcinogenic potential, (S,S)EDDS was determined not likely to be carcinogenic to humans at low doses.
U. S. EPA *Diflubenzuron; Pesticide Tolerances for Emergency Exemptions*	This regulation establishes time-limited tolerances for combined residues of diflubenzuron and its metabolites p-chlorophenylurea and p-chloroaniline in or on alfalfa, forage, and alfalfa hay. p-Chloroaniline tested positive for splenic tumors in male rats and hepatocellular adenomas/carcinomas in male mice in an NTP study (TR-351 – Toxicology and Carcinogenesis Studies of para-Chloroaniline Hydrochloride (1989).
U. S. EPA *Residues of Silver in Foods from Food Contact Surface Sanitizing Solutions; Exemption from the Requirement of a Tolerance*	TER-20001 – the no-observed-adverse-effect level (NOAEL) recorded for developmental toxicity in rats receiving gavage doses of silver acetate exceeded 100 mg/ kg when the test material was administered on gestational days 6-19.
U. S. EPA *Sixty-Fourth Report of the Toxic Substances Control Act Interagency Testing Committee to the Administrator of the Environmental Protection Agency*	NTP Workshop: Developing Experimental Approaches for Evaluation of Toxicological Interactions of Nanoscale Materials (2004).
U. S. EPA *Amine Salts of Alkyl (C8-C24) Benzenesulfonic Acid (Dimethylaminopropylamine, Isopropylamine, Mono-, Di-, and Triethanolamine); Exemption from the Requirement of a Tolerance*	TOX-20 – Toxicity Studies of Diethanolamine Administered Topically and in Drinking Water to F344/N Rats and B6C3F1 Mice (1992).
U. S. FDA *Acrylamide in Food; Request for Comments and for Scientific Data and Information*	NTP/NCTR in 2002 embarked on a series of new toxicology assays for acrylamide. These include long-term carcinogenicity bioassays of acrylamide and its metabolite glycidamide in mice and rats, as well as studies on toxicokinetics, bioavailability, mutagenicity, and neurodevelopment. NCTR's work also includes developing a physiologically based pharmacokinetic model for acrylamide and glycidamide.
OSHA *Occupational Exposure to Diacetyl and Food Flavorings Containing Diacetyl*	The NTP has approved the nomination of butter flavoring, diacetyl, and acetoin for long term inhalation testing.
U. S. FDA *FDA-Regulated Products that Contain Bisphenol-A; Request for Information*	NTP-CERHR Monograph on Bisphenol A (2008).

A complete listing of NTP studies used by Federal and state regulatory agencies is at: *http://ntp.niehs.nih.gov/go/regact*

Nomination, Selection, Evaluation, and Review

Nominations for Study

The NTP maintains a balanced research and testing program that provides data addressing a wide variety of issues important to public health. The NTP actively seeks to identify and select for study chemicals and other substances for which sufficient information is not available to adequately evaluate potential human health hazards. The NTP accomplishes this goal through a formal open nomination and selection process. Substances considered appropriate for study generally fall into two broad, yet overlapping, categories:

1. Substances judged to have high concern as a possible public health hazard based on the extent of human exposure and/or suspicion of toxicity.
2. Substances for which toxicological data gaps exist and additional studies would help assess potential human health risks, e.g., by extrapolating data across species or by evaluating dose-response relationships.

Input is also solicited regarding the nomination of studies that test hypotheses to enhance the predictive ability of future NTP studies, address mechanisms of toxicity, or fill significant gaps in the knowledge of the toxicity of classes of chemical, biological, or physical substances. Increased efforts continue to focus on:

- Improving the quality of the nominations of chemicals, environmental agents, or issues for study so that public health and regulatory needs are addressed.
- Broadening the base and diversity of nominating organizations and individuals.
- Increasing nominations for studying non-cancer toxicological end points.

The nomination process is open to the public. The NTP routinely solicits nominations at conferences and workshops; through the NTP newsletter, *Federal Register* notices, the NTP homepage (*http://ntp.niehs.nih.gov*), and from interested individuals and groups. Also, NCI, FDA, NIOSH, and NIEHS routinely select and forward nominations to the NTP. The NTP also reviews environmental occurrence and human exposure databases and the scientific literature to identify substances of potential interest.

Contact Information: Office of Nomination and Selection, Dr. Scott Masten, *masten@niehs.nih.gov.*
Nomination website: *http://ntp.niehs.nih.gov/* select "Nominations to the Testing Program."

Review and Selection Process

Reviewing and selecting substances and issues nominated for study is a multi-step process (see figure 5 and *http://ntp.niehs.nih.gov/go/156*) that addresses a broad range of concerns from participating representatives from the NIEHS, other Federal agencies, the NTP Board of Scientific Counselors (see page 7), the NTP Executive Committee (see page 11), and the public. This multi-step evaluative process provides the NTP with direction and guidance to ensure that its testing program addresses toxicological concerns in all areas of public health and that there is balance among the types of substances selected for study (e.g., industrial chemicals, consumer products, therapeutic agents). Figure 5 summarizes the study nomination review process, and Table 12 lists the nominations reviewed in FY 2009.

Fig. 5

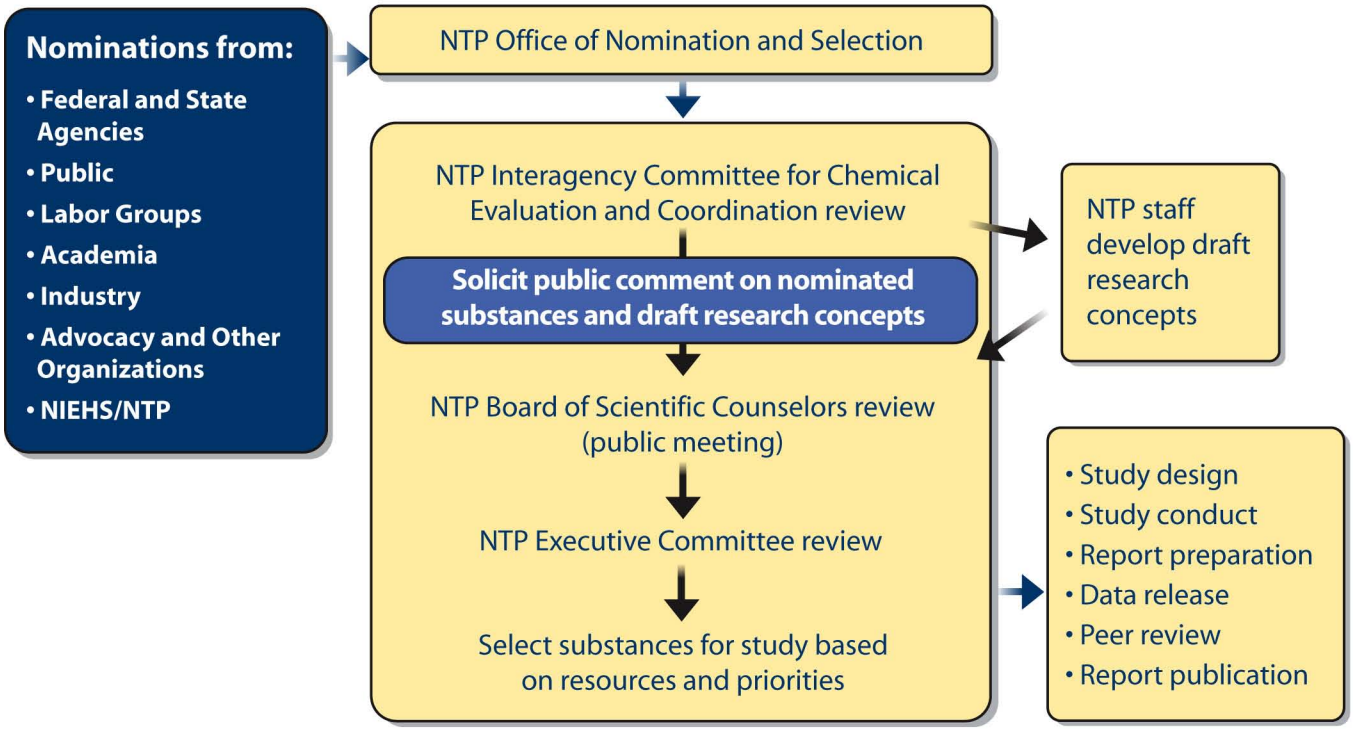


Table 12: Nominations Reviewed in FY 2009

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
Alkylanilines 2-Ethylaniline [578-54-1] 3-Ethylaniline [587-02-0] 3,5-Dimethylaniline [108-69-0]	NIEHS	• Potential for human exposure from a variety of industrial and ambient sources • Suspicion of toxicity based on chemical structure • Insufficient data to characterize toxicity of this aniline subclass	• Initial toxicological 2-Ethylaniline characterization
Butterbur [no CASRN]	NIEHS	• Use as a dietary supplement • Lack of toxicological data • Suspicion of toxicity based on pharmacological activity of constituents • Potential presence of hepatotoxic pyrrolizidine alkaloids	• Comprehensive toxicological characterization • Variable composition critical to consider in selecting test material • Consider "active" constituents for individual toxicity studies

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
1-Chloro-4-(trifluoromethyl)benzene [98-56-6]	Kowa American Corp.	• High production volume • Increasing industrial and potential consumer use • Lack of workplace exposure standards • Lack of chronic toxicity data	• Comprehensive toxicological characterization including developmental and reproductive toxicity and chronic toxicity/ carcinogenicity studies
Deoxynivalenol [51481-10-8]	NIEHS	• Widespread environmental occurrence and potential for human exposure through consumption of contaminated foods • Demonstrated toxicological activity • Lack of definitive carcinogenicity and reproductive toxicity studies	• Comprehensive toxicological characterization including reproductive toxicity and chronic toxicity/ carcinogenicity studies
Dong quai (*Angelica sinensis* root [308068-61-3] and extract [299184-76-2])	Private Individual	• Widespread use as a dietary supplement • Suspicion of toxicity based on estrogenic activity and chemical structure • Lack of adequate toxicity data	• Comprehensive toxicological characterization including phototoxicity studies
Drinking water disinfection by-products: New and emerging chemical classes – • Haloquinones: 2,6-dichloro-1, 4-benzoquinone [697-91-6] • Halopropanones: 1,1-dichloropropanone [513-88-2] and 1,1,1-trichloropropanone • Haloaldehydes: dichloroacetaldehyde and 2-chloropropenal • Halonitriles: 2,2-dichloropropionitrile and 2,3-dichloropropenenitrile • Alkaloidal nitrosamines: *N*-nitroso-3-methylindole • Organic *N*-chloramines: *N,N'*-dichlorolysine and *N,N'*-dichlorohistamine	Private Individual	• Potential or known occurrence in finished (chlorinated and/or chloraminated) drinking water • Strong suspicion of toxicity based on structure-activity considerations • Lack of adequate toxicity data	• Toxicological characterization • Consult with relevant EPA offices/laboratories to determine data needs and then develop a coordinated research strategy to address those needs • ICCEC acknowledged that continued research in this area is important and endorsed investing NTP time and resources to engage EPA and other interested stakeholders in further developing appropriate research programs; participation in Gordon Conferences suggested
Drinking water disinfection by-products: Sodium bromate [7789-38-0]	Private Individual	• Known occurrence in finished (ozonated) drinking water • Renal carcinogen in male rats • Insufficient data on carcinogenic dose-response, toxicokinetics, and mode of action across species/strain/sex	• Carcinogenicity studies • Consult with relevant EPA offices/laboratories to design a research program to meet agency needs
Drinking water disinfection by-products: HMG-CoA reductase inhibition and developmental toxicity	Private Individual	• Co-occurrence in drinking water of therapeutic drugs, environmental contaminants, and disinfection by-products with known developmental and/or reproductive toxicities • Inadequate data to understand potential hazard of mixed exposures	• Mechanistic studies • Interactive effects of prenatal exposure to statins and dichloracetic acid on HMG-CoA reductase and developmental effects

Substance [CASRN]	Nominator	Nomination Rationale	Study Recommendation
Drinking water disinfection by-products: Interactive effects of anti-lipidemic agents and drinking water contaminants in producing developmental toxicity	Private Individual	• Co-occurrence in drinking water of therapeutic drugs, environmental contaminants, and disinfection by-products with known developmental and/or reproductive toxicities • Inadequate data to understand potential hazard of mixed exposures	• Mechanistic studies • Use HMG-CoA reductase study to inform design of a broader mixture study to include other water contaminants that affect lipid metabolism and produce developmental toxicities by similar but different modes of action
Evening primrose oil [90028-66-3]	NIEHS	• Use as a dietary supplement, particularly for autoimmune conditions • Lack of adequate toxicological data	• Initial toxicological characterization • Immunotoxicity studies • Need to identify possible "active" constituents other than polyunsaturated fatty acids
Hydroquinone [123-31-9]	FDA	• Use in drugs and cosmetics • Evidence of carcinogenicity from oral exposures in prior NTP studies • Insufficient toxicological data for regulatory hazard determination	• Dermal toxicity and carcinogenicity studies using over-the-counter concentrations • Reproductive toxicity studies • Dermal studies in animals with functioning melanocytes • Combine studies with existing studies of arbutin
Indium tin oxide [50926-11-9]	NIEHS	• Increasing production and use; documented pulmonary effects in exposed workers • Suspicion of toxicity based on chemical structure • Lack of adequate toxicity data	• Comprehensive toxicological characterization
Silica flour [14808-60-7]	Private individual	• Used in skin care and pharmaceutical products • Inhalation exposures associated with autoimmune disease • Lack of toxicity data for oral and dermal exposures • Insufficient data to evaluate dose-response for renal and autoimmune effects by any route of exposure	• Initial toxicological characterization via oral and dermal routes of administration • Immunotoxicity studies • Exposure levels for toxicity studies should include upper limit of dose expected from use of consumer products • Need criteria for selecting appropriate test material (source, purity, size, coating)
Tris(4-chlorophenyl)methane [27575-78-6] Tris(4-chlorophenyl)methanol [3010-80-8]	NIEHS	• Widespread occurrence and persistence in the environment • Suspicion of toxicity based on anti-androgenic activity • Lack of adequate toxicity data	• Initial toxicological characterization
Valerian (*Valeriana officinalis* L.) [8057-49-6], extracts and oil [8008-88-6]	NIEHS	• Use as a dietary supplement • Lack of toxicological data • Concern for adverse developmental and reproductive effects	• Comprehensive toxicological characterization • Need to survey what botanical (subspecies/cultivar) is marketed as dietary supplement

Evaluation

In carrying out its mission, the NTP provides toxicological evaluations on substances of public health concern. The NTP can initiate bioassays to characterize potential carcinogenicity of only a small fraction of the thousands of substances for which there is little or no information. Many more substances are also studied to assess a variety of non-cancer health-related effects including, but not limited to, reproductive and developmental toxicities, immunotoxicity, neurotoxicity, and genotoxicity. Other biological parameters are often assessed, such as quantifying the disposition and excretion of substances, identifying and correlating biochemical markers with exposure and metabolism, and examining genetic polymorphisms in human drug metabolizing enzymes to understand the susceptibility of individuals and populations to xenobiotic-induced toxicity.

An NTP project review committee evaluates a study's project plan (e.g., design, methods, hypothesis, etc.). The toxicological evaluation for carcinogenicity generally involves repeated administration of a substance to groups of laboratory animals for up to two years. Many short-term, subchronic studies are designed to provide dose-setting information for longer, chronic exposure studies and to address specific gaps in the toxicology database. The adverse health effects from short- or long-term exposures to different dose levels of a substance are examined by observation, histopathology, and several toxicology end points, comparing them with control groups of animals not exposed to the substance. Many substances are also studied using protocols specifically designed to address how the substance causes particular toxic effects. The NTP has specific requirements that testing laboratories comply with the Animal Welfare Act of 1966 and adhere to the principles in the "*Guide for the Care and Use of Laboratory Animals*" (NRC, 1996). General information about the objectives and procedures of NTP study protocols is available on the NTP website (*http://ntp.niehs.nih.gov/* select "Descriptions of NTP Study Types"). Current testing status can be found at *http://ntp.niehs.nih.gov:8080/index.html?col=010stat*.

The NTP carries out toxicology and carcinogenesis testing through two primary mechanisms: laboratory studies conducted in contract laboratories (see table 13) and studies conducted via IAGs at agencies (see page 77). In addition to toxicology research on compounds and exposures, the NTP supports developing new techniques and methods to improve the ability to identify and assess potential environmental toxicants and to develop and validate novel and alternative testing methods that will reduce, replace, or refine animal use. The NTP also supports developing improved statistical methods for designing and evaluating the results of toxicology studies.

Table 13: NTP Contracts that Support NTP Testing Activities

Description	Contractor
ADME chemical disposition in mammals	Lovelace Biomedical and Environmental Research
ADME chemical disposition in mammals	Research Triangle Institute
Cell phone radio frequency	IIT Research Institute
Central data management and information services	Z-Tech Corporation
Chemical disposition in mammals	University of Arizona
Chemistry support services	Battelle Memorial Institute
Chemistry support services	Midwest Research Institute
Chemistry support services	Research Triangle Institute
Evaluate health effects of chemicals in animals	Research Triangle Institute
Genetic toxicity in bacteria and rodents	Integrated Laboratory Systems
HTS for immunotoxicology using HALO-384	Hemogenix
Investigative research support	Integrated Laboratory Systems

Molecular oncology and toxicology support	Integrated Laboratory Systems
NIEHS archives and specimen repository	Experimental Pathology Labs
NTP nomination and background information	Integrated Laboratory Systems
NTP statistical and computer support	Constella Group
NTP technical reports preparation services	Biotechnical Services, Inc.
Pathology support for the NIEHS	Integrated Laboratory Systems
Pathology support for the NTP	Charles River
Pathology support for NTP quality assurance	Experimental Pathology Labs
QA support for audits and inspections	Dynamac Corporation
Reproductive assessments in rodents	Research Triangle Institute
Research on inhalation toxicology	Alion Science and Technology
Toxicological potential of selected chemicals	Battelle Memorial (Pacific NW)
Toxicological potential of selected chemicals	BioReliance
Toxicological potential of selected chemicals	Southern Research Institute

Review and Dissemination

The results of toxicology and carcinogenesis studies undergo rigorous peer review and are published in several NTP report series:

- Technical Reports (TR). This series presents the results of long-term, generally 2-year, toxicology and carcinogenicity studies, typically conducted in rats and mice. Results of genetic toxicology, ADME, and toxicokinetic studies are often included in the reports. The Technical Reports Review Subcommittee of the NTP BSC (see Advisory Boards and Committees, page 7) evaluates the draft reports at a public meeting.

- NTP Toxicity (TOX) Reports. TOX reports are prepared for studies where the substance exposure period is short term, generally up to 13 weeks. Draft reports are typically peer reviewed by letter review.

- Genetically Modified Models (GMM) Reports. NTP began the GMM report series in May 2003. This report series presents the results of substances evaluated by NTP in transgenic mouse strains (e.g., p53+/- heterozygous and Tg.AC mice). The Technical Reports Review Subcommittee of the NTP BSC (see Advisory Boards and Committees, page 7) evaluates draft GMM reports at a public meeting.

Abstracts of the TR, TOX, and GMM series are posted on the NTP website, and PDF files of completed reports are available at the NTP website (*http://ntp.niehs.nih.gov/go/reports*) and are also catalogued in PubMed. Pathology data from the NTP rodent studies included in these reports undergo several reviews. The final review is by the pathology working group (PWG), a panel of experts convened by the NTP to review the microscopic evaluations. After the NTP PWG review, pathology tables and body weight and survival graphs for the completed studies are made publicly available (*http://ntp.niehs.nih.gov/go/peerreview*) until draft study reports are completed for peer review. When the draft reports are completed for peer-review, the abstracts are put on the NTP website with the list of reports. The pathology tables and the body weight and survival graphs are accessible at the end of the abstract text. Following peer review, the NTP finalizes the report, posts it on its website (*http://ntp.niehs.nih.gov/go/reports*) and provides electronic links to the final pathology tables and the curves for body weight and survival. Study summaries for other types of studies, such as immunotoxicity, developmental toxicity, and

reproductive toxicity studies, are also available on the "NTP Study Reports" page on the website. Once the new criteria for immunotoxicity, developmental, and reproductive studies are finalized (see page 42) the NTP will also publish these studies as technical reports following peer review. All types of NTP studies may also be published in peer-reviewed scientific journals.

Chronic Toxicity/Carcinogenicity Studies

In the area of general toxicology assessments, the scope and types of studies performed are dictated mainly by the data needs for the specific substance being studied. General toxicology studies usually fall into two categories: subchronic or pre-chronic studies, and 2-year chronic toxicology and carcinogenicity studies. Two-year studies in rodents are a method by which chemicals or physical agents are identified as having the potential to be hazardous to humans.

The chronic toxicology and carcinogenicity studies in conventional rodent models generally use both male and female rats (Fischer 344/N, Harlan Sprague Dawley, or Wistar Han) and mice (B6C3F1 hybrid), with three exposure levels plus untreated controls, in groups of 50 animals, for two years; other rodent models (e.g., genetically modified mice) are used as needed. If adequate data exist in the literature for one rodent species (rats or mice), then typically only the remaining species is studied. The NTP interfaces its testing with regulatory agencies and the private sector to minimize duplication of effort. Studies ongoing, initiated, completed, and published in FY 2009 are listed in Tables 14, 15, 16, and 17, respectively.

The NTP describes the results of individual experiments on a chemical agent and notes the strength of evidence for conclusions of each study. Negative results, in which the study animals do not have a greater incidence of neoplasia than do control animals, do not necessarily mean that a chemical is not a carcinogen, because the experiments are conducted under a limited set of conditions. Positive results demonstrate that a chemical is carcinogenic for laboratory animals under the conditions of the study and indicate that exposure to the chemical has the potential to be hazardous to humans.

Table 14: Ongoing Chronic Toxicity/Carcinogenicity Studies during FY 2009					
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Study Length**	**Project Leader**
Acrylamide	[79-06-1]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Aloe vera whole leaf extract (native)		Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Boudreau
Antimony trioxide	[1309-64-4]	Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Stout
3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
*3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	9 months	Leakey
AZT/drug combinations transplacental/ neonatal study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Gavage	2 years	Beland
AZT/drug combinations transplacental carcinogenesis study		Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	*In Utero*	2 years	Beland
Bromodichloroacetic Acid	[71133-14-7]	Rats: F344/NTac Mice: B6C3F1	Water	2 years	Hooth
1-Bromopropane	[106-94-5]	Rats: F344/N Mice: B6C3F1	Inhalation	2 years	Morgan
bis (2-Chloroethoxy)methane	[111-91-1]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Dunnick
Cobalt	[7440-48-4]	Rats: F344/NTac Mice: B6C3F1	Inhalation	2 years	Hooth
Diethylamine	[109-89-7]	Rats: F344/N Mice: B6C3F1	Inhalation	2 years	Morgan
N,N-Dimethyl-p-toluidine	[99-97-8]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Dunnick
Ginkgo biloba extract	[90045-36-6]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Chan
Ginseng	[50647-08-0]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Chan
Glycidamide	[5694-00-8]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Water	2 years	Beland
Green tea extract		Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Chan
Indole-3-carbinol	[700-06-1]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	2 years	Wyde
Kava kava extract	[9000-38-8]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Behl/Chan
Metalworking fluids (CIMSTAR 3800)		Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan
Methyl *trans*-styryl ketone	[1896-62-4]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Cunningham
Milk thistle extract	[84604-20-6]	Rats: F344/N Mice: B6C3F1	Feed	2 years	Dunnick

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Pentabromodiphenyl oxide (technical) (DE 71)	[32534-81-9]	Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Dunnick
beta-Picoline	[108-99-6]	Rats: F344/N Mice: B6C3F1	Water	2 years	Wyde
Pulegone	[89-82-7]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Auerbach
Pyrogallol	[87-66-1]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Mercado-Feliciano
All-*trans*-retinyl palmitate	[79-81-2]	Mice: SKH-1 Hairless	Topical application	2 years	Boudreau
Styrene-acrylonitrile trimer		Rats: F344/N	Feed	2 years	Behl/Chhabra
Tetrabromobisphenol A	[79-94-7]	Rats: Wistar Han Mice: B6C3F1	Gavage	2 years	Dunnick
alpha/beta Thujone mixture	[50647-08-0]	Rats: F344/N Mice: B6C3F1	Gavage	2 years	Hooth
Trimethylolpropane triacrylate	[15625-89-5]	Rats: F344/N Mice: B6C3F1	Topical application	2 years	Surh/Chhabra
Vinylidene chloride	[75-35-4]	Rats: F344/N Mice: B6C3F1	Inhalation	2 years	Wyde

Table 15: Chronic Toxicity/Carcinogenicity Studies Initiated FY 2009

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Aging Cohort Study – Co129/SvImJ mouse		Mice: 129S1/SvImJ	Not applicable	2 years	French
Aging Cohort Study - B6C3F1J mouse		Mice: B6C3F1 (Jackson)	Not applicable	2 years	French
Aging Cohort Study - C3H/HeJ mouse		Mice: C3H/HeJ	Not applicable	2 years	French
Aging Cohort Study - C57/BL/6J mouse		Mice: C57BL/6J (Jackson)	Not applicable	2 years	French
Aging Cohort Study - A/J mouse		Mice: A/J	Not applicable	2 years	French
2,3-Butanedione	431-03-8	Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan
Furan	110-00-9	Rats: F344/N	Gavage	2 years	Beland
Metal working fluids (Trim VX)		Rats: Wistar Han Mice: B6C3F1	Inhalation	2 years	Morgan
Perfluorooctanoic acid (PFOA)	[335-67-1]	Rats: Harlan Sprague Dawley	Feed	2 years	Blystone
Zinc carbonate, basic	[5263-02-5]	Rats: Harlan Sprague Dawley	Feed	2 years	Wyde

Table 16: Technical Reports Completed during FY 2009

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Androstenedione – Gavage	[63-05-8]	TR-560	A natural androgen steroid hormone synthesized in both men and women. It is an intermediate in the pharmaceutical synthesis of testosterone and other steroids, including oral contraceptives and topical anti-inflammatory products. It was also used as a dietary supplement by athletes before over-the-counter sales were banned.
Goldenseal root powder – Feed		TR-562	Folk medicine for treating gastrointestinal disturbances, urinary disorders, hemorrhage, inflammation, and skin, mouth, and eye infections.
beta-Myrcene – Gavage	[123-35-3]	TR-557	Intermediate in the commercial production of terpene alcohols, which serve as intermediates for producing large-volume aroma and flavor chemicals, and used as scenting agents in cosmetics, soaps, and detergents. beta-myrcene is a peripheral analgesic substance and the active ingredient in lemongrass tea. It has been identified in> 200 plants and detected in emissions of plywood veneer dryers.
2,3′,4,4′,5-Pentachlorobiphenyl (PCB 118) – Gavage	[31508-00-6]	TR-559	One of the banned polychlorinated biphenyls formerly used as an industrial insulator and lubricant. Studied as part of the dioxin toxic equivalency factor evaluation.
3,3′,4,4′-Tetrachloroazobenzene – Gavage	[14047-09-7]	TR-558	An impurity formed as an unwanted by-product in the manufacture of 3,4-dichloroaniline and its herbicidal derivatives Propanil®, Linuron®, and Diuron®. It occurs from the degradation of chloroanilide herbicides (acylanilides, phenylcarbamates, and phenylureas) in soil by peroxide-producing microorganisms and is formed by the photolysis and biolysis of 3,4-dichloroaniline.
Tetralin – Inhalation	[119-64-2]	TR-561	An industrial solvent mainly for naphthalene, fats, resins, oils, and waxes; as a solvent and stabilizer for shoe polishes and floor waxes; as a solvent for pesticides, rubber, asphalt, and aromatic hydrocarbons; as a dye solvent carrier in the textile industry; as a substitute for turpentine in lacquers, paints, and varnishes; in paint thinners and as a paint remover; in alkali-resistant lacquers for cleaning printing ink from rollers and type; as a constituent of motor fuels and lubricants; for the removal of naphthalene in gas distribution systems; and as an insecticide for clothes moths.

Table 17: Technical Reports Published during FY 2009

Chemical/Exposure–Study Type	[CASRN]	Technical Report Number	Use
Cumene – Inhalation	[98-82-8]	TR-542	The principal chemical used in the production of phenol and acetone and to produce acetophenone, α-methylstyrene, diisopropylbenzene, and dicumylperoxide. It is also used as thinner; a constituent of some petroleum-based solvents; in gasoline blending, diesel fuel, and high-octane aviation fuel; and as a raw material for peroxides and oxidation catalysts. Because cumene is a good solvent for fats and resins, it has been suggested as a replacement for benzene in many industrial applications. Cumene occurs naturally in petroleum and in a variety of foodstuffs.
Bromochloroacetic Acid – Feed	[5589-96-8]	TR-549	A water disinfection by-product.

Note: Only summaries of carginogenicity conclusions are included in the tables. Complete information is available in the full study reports found at *http://ntp.niehs.nih.gov/*.

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Equivocal evidence	Equivocal evidence	Clear evidence	Clear evidence
Clear evidence	Clear evidence	Some evidence	No evidence
Clear evidence	Equivocal evidence	Clear evidence	Equivocal evidence
Not tested	Clear evidence	Not tested	Not tested
Clear evidence	Clear evidence	Clear evidence	Clear evidence
Some evidence	Some evidence	No evidence	Equivocal evidence

Levels of Evidence of Carcinogenic Activity			
Male Rats	Female Rats	Male Mice	Female Mice
Clear evidence	Some evidence	Clear evidence	Clear evidence
Clear evidence	Clear evidence	Clear evidence	Clear evidence

CLEAR Evidence SOME Evidence EQUIVOCAL Evidence NO Evidence

The NTP anticipates that six Technical Reports will undergo peer review in FY 2010, as shown in Table 18.

Table 18: Technical Reports Planned for Peer Review in FY 2010

Chemical	Technical [CASRN] Number	Report	Use
1-Bromopropane – Inhalation	[106-94-5]	TR-564	Used in the early to mid-1990s mainly as an intermediate in producing pesticides, quaternary ammonium compounds, flavors and fragrances, pharmaceuticals, and other chemicals in well-controlled, closed processes. In the mid to late 1990s, it was introduced as a less toxic replacement for methylene chloride in emissive applications such as vapor and immersion degreasing operations and critical cleaning of electronics and metals. 1-Bromopropane was also introduced as a nonflammable, nontoxic, fast-drying, and inexpensive solvent for adhesive resins, and has been marketed as a replacement for ozone-depleting refrigerants.
bis(2-Chloroethoxy)methane – Dermal	[111-91-1]	TR-536	Used as a solvent and the starting agent in the production of fungicides and polysulfide polymers.
Diethylamine – Inhalation	[109-87-7]	TR-566	Used mainly as a chemical intermediate to produce the corrosion inhibitor N,*N*-diethylethanolamine, and a lesser amount is used to produce pesticides and insect repellants and in rubber processing.
Ginseng – Gavage	[50647-08-0]	TR-567	A perennial aromatic herb widely used in herbal remedies, dietary supplements, cosmetics, and as a food additive.
Milk thistle extract – Feed	[84604-20-6]	TR-565	Used as a medicinal herb for treating liver cirrhosis, chronic hepatitis (liver inflammation), and gallbladder disorders. Treatment claims also include lowering cholesterol levels; reducing insulin resistance; reducing the growth of cancer cells in breast, cervical, and prostate cancers; and antiviral activity. Other reported uses of milk thistle in folk medicine include treating malarial fever, bronchitis, gallstones, jaundice, peritonitis, uterine congestion, and varicose veins and to stimulate milk for nursing mothers. The roots soaked in water overnight are used in food, and the despined leaves are added to salads. Roasted milk thistle fruit has been used as a coffee substitute.
Pulegone – Gavage	[89-82-7]	TR-563	Major constituent of pennyroyal. Several essential oils contain pulegone and are used for flavoring foods, drinks, and dental products, as fragrance agents, and in herbal medicines.

General Toxicology Studies

The NTP performs prechronic toxicity studies to address specific deficiencies in toxicology databases for chemicals, such as an understanding of toxicity with repeated exposures; to identify target organs for more in-depth systems toxicology evaluations and mechanistic studies; and to provide dose-setting information for possible chronic studies.

Although designs are flexible, prechronic studies usually involve exposures of rats and mice of both sexes to substances for periods of 14-90 days. Assessments almost always include tissue histopathology, clinical pathology, and sperm motility or measurements of estrous cycle length. The frequency of malformed red blood cells (micronucleated erythrocytes, a measure of chromosomal damage) is determined as an *in vivo* measure of genotoxic potential.

The study protocol may include more detailed or focused studies when findings published in the existing scientific literature or identified in initial NTP studies suggest a target organ or system. The study protocol may include separate studies of reproductive, genetic, or immunological toxicity based on the outcome of the toxicity screens and may use additional end points to improve our understanding of the mechanisms and modes of action of a chemical.

In some cases, the NTP uses alternative models, including genetically modified mouse models and non-mammalian models, for prechronic studies. Such studies are presented in the section "Genetic and Alternative Test Systems" (page 72). Tables 19-21 list the toxicity studies that were ongoing, initiated, and completed, respectively, during FY 2009. Information is available at *http://ntp.niehs.nih.gov/go/reports*. Table 22 lists toxicity studies planned for FY 2010.

Table 19: Ongoing Toxicity Studies during FY 2009

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
*3′-Azido-3′-deoxythymidine (AZT)	[30516-87-1]	Mice: P53 +/- (FVB/N)	Gavage	9 months	Leakey
QT drugs (bepridil hydrochloride)	[74764-40-2]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (diltiazem hydrochloride)	[33286-22-5]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (loratadine)	[79794-75-5]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (lovastatin)	[75330-75-5]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (sotalol hydrochloride)	[959-24-0]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
QT drugs (terfenadine)	[50679-08-8]	Dogs: Beagles	Oral (capsule)	1 day	Hooth
(+)-Usnic acid	[7562-61-0]	Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 90 days	Leakey

Table 20: Toxicity Studies Initiated during FY 2009

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Abrasive blasting agents (blasting sand)		Rats: Harlan Sprague Dawley Rats: F344/NTac	Inhalation	39 weeks 14 days	Roycroft
Abrasive blasting agents (specular hematite)		Rats: Harlan Sprague Dawley Rats: F344/NTac	Inhalation	39 weeks 14 days	Roycroft
Acetoin	[513-86-0]	Rats: Wistar Han Mice: B6C3F1	Inhalation	14 days 90 days	Morgan
Cell phone radiation (CDMA [Code Division Multiple Access] technology)		Rats: Harlan Sprague Dawley Mice: B6C3F1	Whole-body exposure	5 days 49 days	Wyde
Cell phone radiation (GSM [Global System for Mobile Communication] technology)		Rats: Harlan Sprague Dawley Mice: B6C3F1	Whole-body exposure	5 days 49 days	Wyde
bis(2-Chloroethoxy)methane	[111-91-1]	Mice: B6C3F1	Gavage	3 days	Dunnick
Ephedrine + caffeine combination	[58-08-2] [299-42-3]	Mice: B6C3F1	Gavage	3 days	Dunnick
Glucosamine hydrochloride + chondroitin sulfate	[9007-28-7] [66-84-2]	Rats: Zucker – Obese (HsdHlr: ZUCKER-Leprfa) Rats: Zucker - Lean (HsdHlr: ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
Gum guggul extract		Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	13 weeks	Wyde
Ionic liquid toxicity •1-Butyl-3-methylimidazolium chloride •1-Butyl-1-methylpyrrolidinium chloride •*N*-Butylpyridinium chloride •1-Ethyl-3-methylimidazolium chloride	[1124-64-7] [79917-90-1] [65039-09-0] [479500-35-1]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Water	14 days	Hooth
Metalworking fluids (Syntilo 1023)		Rats: Wistar Han Mice: B6C3F1	Inhalation	13 weeks	Morgan
2-Methoxy-4-nitroaniline	[97-52-9]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Feed	2 weeks 13 weeks	Surh
Myristicin	[607-91-0]	Rats: F344/NTac Mice: B6C3F1	Gavage	13 weeks	Wyde
ortho-Phthalaldehyde	[643-79-8]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Inhalation	90 days	Wyde
Resveratrol	[501-36-0]	Rats: Wistar Han Rats: F344/NTac Mice: B6C3F1	Gavage	2 weeks 13 weeks	Germolec
Serotype 5 Adeno-associated viral vector (rAAV5SCTLA4: Ig)		Mice: BALB/c	Intraductal cannulation	13 weeks	Irwin
Sodium tungstate, dihydrate	[10213-10-2]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Water	13 weeks (perinatal) 13 weeks	Hooth
tris(2-Chloroisopropyl) phosphate	[13674-84-5]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Feed	90 days	Stout
Usnea lichen		Rats: F344 (NCTR) Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Feed	2 weeks 90 days	Leakey

Table 21: Toxicity Studies Completed during FY 2009

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Acetoin	[513-86-0]	Rats: Wistar Han Mice: B6C3F1	Inhalation	14 days	Morgan
Black cohosh	[84776-26-1]	Rats: Wistar Han	Gavage	13 weeks	Mercado-Feliciano
2,3-Butanedione	[431-03-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	90 days	Morgan
bis(2-Chloroethoxy)methane	[111-91-1]	Mice: B6C3F1	Gavage	3 days	Dunnick
Di(2-ethylhexyl) phthalate	[117-81-7]	Monkey: Rhesus	Intravenous injection and oral	14 days	Delclos
Ephedrine + caffeine combination	[58-08-2] [299-42-3]	Mice: B6C3F1	Gavage	3 days	Dunnick
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)- (Iso-E Super)	[54464-57-2]	Rats: F344/NTac Mice: B6C3F1	Topical application	13 weeks	Chan
Metalworking fluids (Syntilo 1023)		Rats: Wistar Han Mice: B6C3F1	Inhalation	13 weeks	Morgan
Metalworking fluids (Trim VX)		Rats: Wistar Han Mice: B6C3F1	Inhalation	13 weeks	Morgan
Microcystin-LR (TGMX)	[101043-37-2]	Rats: Wistar Han	Intravenous	1/2/6/24 hrs	Walker
Nanoscale material (fullerene-C60 1 µm)	[99685-96-8]	Rats: Wistar Han, Mice: B6C3F1	Inhalation	90 days	Walker
Nanoscale material (fullerene-C60 50 nm)	[99685-96-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	90 days	Walker
Nanoscale material (quantum dots)		Mice: SKH-1 Hairless (NCTR)	Topical application	2 weeks	Howard
ortho-Phthalaldehyde	[643-79-8]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Inhalation	90 days	Wyde
Serotype 2 Adeno-associated Viral Vector rAAV2rapahEpo		Mice: BALB/c	Intraductal cannulation	13 weeks	Irwin
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	Rats: Sprague Dawley	Gavage	18 days 5 weeks	Behl
p-Toluenesulfonamide	[70-55-3]	Rats: F344/NTac Mice: B6C3F1	Feed	2 weeks 13 weeks	Dunnick

Toxicity Study Completed during FY2009 Using a Genetically Modified Model

Chemical	[CASRN]	Species/Strain	Route	Study Length	Project Leader
Nanoscale material (rutile titanium dioxide)	[1317-80-2]	Mice: Tg.AC (FVB/N) Hemizygous	Topical application	2 weeks	Howard

Table 22: Toxicity Studies Planned for FY 2010*					
Chemical	**[CASRN]**	**Species/Strain**	**Route**	**Study Length**	**Project Leader**
Bisphenol A	[80-05-7]	Rats: Harlan Sprague Dawley	Gavage	90 days	Delclos
Black cohosh	[84776-26-1]	Mice: B6C3F1	Gavage	90 days	Mercado-Feliciano
bis(2-Chloroethoxy)methane	[111-91-1]	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson)	Gavage	3 days 10 days	Dunnick
p-Chloro-a,a,a-trifluorotoluene	[98-56-6]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Inhalation	90 days	Stout
Ephedrine + caffeine combination	[58-08-2] [299-42-3]	Mice: C57BL/6J (Jackson) Mice: C3H/HeJ Mice: B6C3F1 (Jackson),	Gavage	3 days 10 days	Dunnick
Glucosamine	[3416-24-8]	Rats: Zucker - Obese (HsdHlr: ZUCKER-Leprfa) Rats: Zucker - Lean (HsdHlr: ZUCKER-Lepr+)	Gavage	13 weeks	Leakey
Insertional mutagenesis (radiation levels)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Whole-body exposure	8 weeks	Irwin
Insertional mutagenesis II (SIN vector)		Mice: B6.SJL-Ptprc[a] Pepc[b]/BoyJ	Intravenous	8 plus 3 weeks	Irwin
2-Methoxy-4-nitroaniline	[97-52-9]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Feed	Range finding: 14 days, 90 days	Surh
Vincamine	[1617-90-9]	Rats: Harlan Sprague Dawley	Gavage	2 weeks	Chan

**Known test articles as of 10/01/2009. Others may be scheduled as protocols are finalized.*

Mutagenesis and Genetic Toxicity

Genetic toxicity test results are used to help interpret toxicity, carcinogenicity, or other *in vivo* test results and to provide a database for use in structure-activity analyses. Analysis of the early, multi-test database showed that positive results for a chemical in the *Salmonella* gene mutation assay were sometimes correlated with carcinogenicity in several species/sexes of rodents and at several tissue sites. Subsequently, studies of the correlation between mutagenicity test data and rodent carcinogenicity showed a strong association between clearly positive results in long-term mouse peripheral blood micronucleus tests and rodent carcinogenicity. The importance of genetic toxicity test data in assessing exposure hazard for NTP chemicals is underscored by the fact that most organic chemicals (other than hormones) identified as human carcinogens by the International Agency for Research on Cancer (IARC) are genotoxic, and the vast majority of them are detected by both the *Salmonella* assay and rodent micronucleus tests. Additional assays may be conducted with certain chemicals to gain further insight into the types of DNA and chromosomal damage induced by a chemical. Substances tested for genetic toxicity during FY 2009 are listed in Table 23. Information is available at (*http://ntp.niehs.nih.gov/go/reports*).

Table 23: Ongoing and Completed Genetic Toxicity Studies during FY 2009		
Chemical	**[CASRN]**	**Testing Battery**
Acetoin	[513-86-0]	Micronucleus
Aloe vera charcoal-filtered whole-leaf extract		*Salmonella*
Aloe vera gel	[8001-97-6]	*Salmonella*
Aloe vera whole-leaf extract (native)		*Salmonella*
2-Aminoanthracene	[613-13-8]	*Salmonella*
Antimony trioxide	[1309-64-4]	Micronucleus
Benzyl chloride	[100-44-7]	*Salmonella*
Black cohosh	[84776-26-1]	Micronucleus
1-Bromopropane	[106-94-5]	*Salmonella*
2,3-Butanedione	[431-03-8]	Micronucleus
1,3-Dichloro-2-propanol	[96-23-1]	Micronucleus
Dimethylamine borane	[74-94-2]	*Salmonella*
2',2'''-Dithiobisbenzanilide	[135-57-9]	*Salmonella*
Epichlorhydrin	[106-89-8]	Micronucleus
Ethanone, 1-(1,2,3,4,5,6,7,8-octahydro-2,3,8,8-tetramethyl-2-naphthalenyl)-(Iso-E Super)	[54464-57-2]	Micronucleus
Ethyl methanesulfonate	[62-50-0]	Micronucleus
Gum guggul extract		Micronucleus
Hydroxyurea	[127-07-1]	Micronucleus
Metalworking fluids (Syntilo 1023)		Micronucleus
Metalworking fluids (Trim VX)		Micronucleus
2-Methoxy-4-nitroaniline	[97-52-9]	*Salmonella*
Milk thistle extract	[84604-20-6]	*Salmonella*
Myristicin	[607-91-0]	Micronucleus
Nanoscale material (fullerene-C60 1 µm)	[99685-96-8]	Micronucleus
Nanoscale material (fullerene-C60 50 nm)	[99685-96-8]	Micronucleus
2-Nitroethanol	[625-48-9]	Micronucleus
2-Nitroethanol	[625-48-9]	*Salmonella*
ortho-Phthalaldehyde	[643-79-8]	Micronucleus
Pentafluoroiodoethane	[354-64-3]	*Salmonella*
Pulegone	[89-82-7]	*Salmonella*
Resveratrol	[501-36-0]	Micronucleus
Senna (powdered)	[8013-11-4]	Micronucleus
Sodium azide	[26628-22-8]	*Salmonella*
Sodium orthovanadate	[13721-39-6]	*Salmonella*
Sodium tungstate, dihydrate	[10213-10-2]	Micronucleus
Sodium vanadate (V)	[13718-26-8]	*Salmonella*
Transgenic model evaluation (cyclophosphamide monohydrate)	[6055-19-2]	Micronucleus
tris(2-Chloroisopropyl)phosphate	[13674-84-5]	Micronucleus
Vincristine sulfate salt	[2068-78-2]	Micronucleus
Water	[7732-18-5]	*Salmonella*
Zinc carbonate, basic	[5263-02-5]	Micronucleus

Organ System Toxicity

Nervous System, Developmental, and Reproductive Toxicity

Behavioral and neurological alterations in response to deleterious environmental agents often represent the earliest evidence of toxicity. These testing batteries examine the sensory, motor, autonomic, and peripheral nervous systems. The Functional Observational Battery employs observational screening, while the NIEHS test battery uses automated test systems to evaluate the various nervous system components.

As part of its charge to test chemicals of concern for potential toxicity, the NTP evaluates developmental and reproductive toxicity primarily by using teratology and Reproductive Assessment by Continuous Breeding (RACB) study designs (see *http://ntp.niehs.nih.gov/go/33668*). The RACB study design was developed by the NTP to identify potential hazards from toxic effects on male and/or female reproduction, to characterize that toxicity, and to define the dose-response relationships for each compound. The study design has evolved over the years: initially the studies mainly used mice as the test species; now, they use rats almost exclusively. As our knowledge has improved and use of sensitive end points has increased, these advances have been incorporated into revisions of the study design.

Table 24 lists completed and ongoing nervous system, developmental, and reproductive studies during FY 2009, and Table 25 lists studies planned for FY 2010.

Table 24: Ongoing and Completed Organ Systems Toxicity Studies during FY 2009

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Bitter orange		Rats: Sprague Dawley	Gavage	Hansen	Teratology
Bitter orange with caffeine		Rats: Sprague Dawley	Gavage	Hansen	Teratology
p-Synephrine	[94-07-5]	Rats: Sprague Dawley	Gavage	Hansen	Teratology
Synephrine and caffeine	[94-07-5] [58-08-2]	Rats: Sprague Dawley	Gavage	Hansen	Teratology
3,3′,4,4′-Tetrachloroazobenzene	[14047-09-7]	Rats: Crl:CD (SD)	Gavage	Hooth	Postnatal developmental toxicity

Table 25: RACB Studies Planned for FY 2010

Chemical	[CASRN]	Species/Strain	Route	Testing Battery
AZT/lamivudine/nevirapine combination	[30516-87-1] [134678-17-4] [129618-40-2]	Mice: Swiss CD-1	Gavage	RACB
n-Butyl glycidyl ether	[2426-08-6]	Rats: Harlan Sprague Dawley	TBD	RACB
n-Butyl-p-hydroxybenzoate	[94-26-8]	Rats: Harlan Sprague Dawley	Gavage	RACB

Immunotoxicity

NTP immunotoxicity studies address adverse effects on the immune system that may result from exposure to environmental chemicals, biological materials, or therapeutic agents. The identification of substances that have potential to cause injury to the immune system is of considerable public health significance as alterations in immune function can lead to increased incidence of hypersensitivity disorders, autoimmune or infectious disease, or neoplasia. Immunotoxicity caused by exposure to chemicals can be divided into two broad research areas: (1) studies of altered hematopoietic (blood cell development) or other immunologic events associated with exposure of humans and animals to chemicals and (2) studies of immune-mediated hypersensitivity (allergy and autoimmunity) resulting from exposure to environmental chemicals or therapeutics. In the former case, the immune system acts as a passive target (nonspecific) for the foreign substance, and the result may be an increased incidence or severity of infectious disease or neoplasia because of the inability to respond adequately to the invading agent. In hypersensitivity (i.e., allergy), the immune system responds to small molecular weight compounds that bind to host tissue, recognizing the complex as foreign antigen. This immune response to the chemical-host tissue complex may lead to diseases, such as respiratory tract allergies (e.g., asthma, rhinitis) or allergic contact (skin) dermatitis. Autoimmunity, another form of immune-mediated disease, is characterized by an immune response against constituents of the body's own tissues (autoantigens). Table 26 lists completed and ongoing immunotoxicity studies during FY 2009.

Table 26: Ongoing and Completed Immunotoxicity Studies during FY 2009

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Abrasive blasting agents (blasting sand)		Rats: Harlan Sprague Dawley	Inhalation	Roycroft	Immunosuppression
Abrasive blasting agents (specular hematite)		Rats: Harlan Sprague Dawley	Inhalation	Roycroft	Immunosuppression
Autumn Sunset True Color Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
3'-Azido-3'-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1	Gavage	Irwin	Immunosuppression, range finding
3'-Azido-3'-deoxythymidine (AZT)	[30516-87-1]	Mice: B6C3F1	Gavage	Irwin	Hypersensitivity
2,3-Butanedione	[431-03-8]	Mice: BALB/c	Topical application	Morgan	Immunosuppression, range finding
2,3-Butanedione	[431-03-8]	Mice: BALB/c	Inhalation	Morgan	Hypersensitivity
tert-Butyl hydroperoxide	[75-91-2]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
o-Cresol	[95-48-7]	Mice: BALB/c	Topical application	Chhabra	Immunosuppression, range finding
Dibenz(a,h)anthracene	[53-70-3]	Mice: B6C3F1	Gavage	Germolec	Developmental
Dibenz(a,h)anthracene	[53-70-3]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, full protocol
1,3-Dichloropropene (Telone II)	[542-75-6]	Mice: B6C3F1	Water	Germolec	Hypersensitivity
Dimethylamine borane	[74-94-2]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Disulfoton	[298-04-4]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, range finding
Double Dark Fudge True Color Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity

Chemical	[CASRN]	Species/Strain	Route	Project Leader	Testing Battery
Double Fudge Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Immunosuppression, full protocol
Echinacea purpurea, extract	[90028-20-9]	Mice: B6C3F1	Gavage	Irwin	Immunosuppression, range finding
Elmiron (sodium pentosanpolysulfate)	[37319-17-8]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, full protocol
Elmiron (sodium pentosanpolysulfate)	[37319-17-8]	Mice: B6C3F1	Gavage	Germolec	Multigeneration
Ethanone, 1-(1,2,3,4,5,6,7, 8-octahydro-2,3,8, 8-tetramethyl- 2-baphthalenyl)- (Iso-E Super)	[54464-57-2]	Mice: BALB/c	Topical application	Chan	Hypersensitivity
Genistein	[446-72-0]	Mice: Nonobese diabetic (NOD)	Gavage	Germolec	Autoimmunity
Gum guggul extract		Mice: B6C3F1	Gavage	Wyde	Immunosuppression, range finding
Heptachlor	[76-44-8]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Ionic liquid (1-butyl- 3-methylimidazolium chloride)	[79917-90-1]	Mice: BALB/c	Topical application	Hooth	Hypersensitivity
Ionic liquid (1-ethyl-3- methylimidazolium chloride)	[65039-09-0]	Mice: BALB/c application	Topical	Hooth	Hypersensitivity
Lovastatin	[75330-75-5]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, range finding
Monoclonal antibody protein therapeutics (CD-4)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression, full protocol
Monoclonal antibody protein therapeutics (CD-8)		Mice: B6C3F1	Intraperitoneal injection	Germolec	Immunosuppression, full protocol
Nanoscale material (fullerene-C60 1 µm)	[99685-96-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	Walker	Immunosuppression, range finding
Nanoscale material (fullerene-C60 50 nm)	[99685-96-8]	Rats: Wistar Han Mice: B6C3F1	Inhalation	Walker	Immunosuppression, range finding
1,5-Naphthalene diisocyanate	[3173-72-6]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Nelfinavir mesylate	[159989-65-8]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, full protocol
Nelfinavir mesylate	[159989-65-8]	Mice: B6C3F1	Gavage	Germolec	Developmental
Nevirapine	[129618-40-2]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, full protocol
Nevirapine	[129618-40-2]	Mice: B6C3F1	Gavage	Germolec	Developmental
Norbixin (cis/trans mixture)	[542-40-5]	Mice: BALB/c	Topical application	Germolec	Hypersensitivity
Phenol	[108-95-2]	Mice: B6C3F1	Water	Germolec	Immunosuppression, full protocol
Resveratrol	[501-36-0]	Mice: B6C3F1	Gavage	Germolec	Immunosuppression, range finding
Rosewood True Color Concentrate		Mice: CBA/Ca Jackson	Subcutaneous injection	Howard	Hypersensitivity
Sodium tungstate, dihydrate	[10213-10-2]	Mice: B6C3F1	Water	Hooth	Immunosuppression, full protocol
3,3',4,4'-Tetrachloroazobenzene	[14047-09-7]	Rats: Sprague Dawley	Gavage	Behl	Immunosuppression, range finding

Disposition, Metabolism and Toxicokinetic Studies

Complete dosimetry of a chemical or physical agent describes its ADME in the body at differing levels of exposure, over all ages, via several routes of exposure, and under varying genetic backgrounds in humans and test animals. Data from NTP chemical disposition and toxicokinetic studies are used in these studies. Substances evaluated during FY 2009 are listed in Table 27, and studies planned for FY 2010 are listed in Table 28. Most studies are conducted in intact laboratory animals; some require incubating human and rodent tissues (liver slices) with the chemical. This information provides dosimetric data that can be combined with other anatomical, biochemical, and physiological information to develop models based on biochemistry and physiologically based pharmacokinetics. Such models are used increasingly in risk assessment to extrapolate between species, across dose ranges, and across different routes of exposure.

Table 27: Ongoing and Completed Disposition, Metabolism and Toxicokinetic Studies during FY 2009

Chemical	[CASRN]	Species/Strain	Route	Project Leader
*Anatase (TiO_2)	[1317-70-0]	Mice: Tg.AC (FVB/N) and FVB/N	Topical application	NCTR
Benzene	[71-43-2]	Mice: • BALB/cByJ • WSB/EiJ *(M. m. domesticus)* • CAST/EiJ *(M. m. castaneus)* • C3H/HeJ • DBA/2 Jackson • BTBR T+ tf/J 2, C57BL/6 • FVB/NJ • KK/HIJ • AKR/J • NZW/LacJ • A/J • NOD/LtJ • B6C3F1 • PWD/PhJ *(M. m. musculus)* • MOLF/EiJ *(M. m. molossinus)* • 129S1/SvImJ	Gavage	Cunningham
2,3-Butanedione	[431-03-8]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Intratracheal	Waidyanatha
2,3-Butanedione	[431-03-8]		*In vitro*	Waidyanatha
2-Butene-1,4-diol	[110-64-5]		*In vitro*	NCTR
n-Butyl-p-hydroxybenzoate	[94-26-8]	Rats: Harlan Sprague Dawley	Topical application	Waidyanatha
Cumene	[98-82-8]	Mice: B6C3F1 Rats: Fischer 344	Gavage	Sanders
1,3-Dichloro-2-propanol	[96-23-1]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Waidyanatha
N,N-Dimethylacetoacetamide	[2044-64-6]	Rats: F344/N Charles River	Gavage	Waidyanatha
Dimethylamine borane	[74-94-2]	Human skin cells Rats: Harlan Sprague Dawley	*In vitro* Intravenous	Waidyanatha
Dimethylethanolamine	[108-01-0]	Mice: B6C3F1 Rats: Wistar	Gavage	Sanders
2',2'''-Dithiobisbenzanilide	[135-57-9]	Rat liver S9	*In vitro*	Sanders
Ephedrine + caffeine combination	[299-42-3] [58-08-2]	Rats: F344	Gavage	Collins
Furan	[110-00-9]	Rats: F344 (NCTR)	Gavage	NCTR
Furan	[110-00-9]	Rats: Tg.Lac1/C57BL/6 (Big Blue)	Gavage	NCTR
Ginkgo biloba extract	[90045-36-6]	Human liver microsomes and hepatocytes	*In vitro*	Cunny

Chemical	[CASRN]	Species/Strain	Route	Project Leader
2-Hydroxy-4-methoxybenzophenone	[131-57-7]	Mice: B6C3F1 Rats: Sprague Dawley	Gavage	Sanders
Isocyanuric acid	[108-80-5]	Rats: Fischer 344	Gavage	NCTR
Melamine	[108-78-1]	Rats: F344 (NCTR)	Gavage	NCTR
Melamine + cyanuric acid combination	[108-78-1] [108-80-5]	Rats: F344 (NCTR)	Feed	NCTR
2-Methoxy-4-nitroaniline	[97-52-9]	Rats: Harlan Sprague Dawley Mice: B6C3F1	Gavage	Waidyanatha
Nanoscale material (fullerene C60)	[99685-96-8]	Rats: F344/N	Intravenous	Sanders
Resveratrol	[501-36-0]	Rats: Wistar	Gavage	Waidyanatha
Sodium dichromate dihydrate(VI)	[7789-12-0]	Rats: F344/N Mice: C57BL/6N	Gavage Water	Waidyanatha
Sodium tungstate, dihydrate	[10213-10-2]	Mice: B6C3F1 Rats: F344/N	Gavage	Waidyanatha
Toxicogenomics study of allylbenzene and propenylbenzene class flavor constituents • Anethole • Estragole • Eugenol • Isoeugenol • Isosafrole • Methyleugenol • Myristicin • Safrole	 [104-46-1] [140-67-0] [97-53-0] [97-54-1] [120-58-1] [93-15-2] [607-91-0] [94-59-7]	Human liver microsomes	*In vitro*	Waidyanatha

**Indicates study conducted using a genetically modified model.*

Table 28: Disposition, Metabolism, and Toxicokinetic Studies Planned for FY 2010

Chemical	[CASRN]	Species/Strain	Route
Isocyanuric acid	108-80-5	Rats: F344 (NCTR)	Gavage
Melamine	108-78-1	Rats: F344 (NCTR)	Intravenous
Melamine cyanurate	37640-57-6	Rats: F344 (NCTR)	Intravenous
Melamine + cyanuric acid combination	108-78-1 108-80-5	Rats: F344 (NCTR)	Dosed, feed
Nanoscale silver	7440-22-4	Rats: Sprague Dawley	Gavage Intravenous
Silver acetate	563-63-3	Rats: Sprague Dawley	Gavage intravenous
Triclosan	3380-34-5	Mice: B6C3F1/NCTR BR (C57BL/6N x C3H/HEN MTV-)	Topical application

Genetic and Alternative Test Systems

Host Susceptibility Program

The NTP's Host Susceptibility Program is focused on the development, testing, and analysis of new *in vivo* and *in vitro* models for investigation of environmentally related exposures and associated disease. The primary aim is to develop new laboratory-based strategies along with models and testing protocols for hazard identification and risk characterization based on quantitative differences in the variable range of response that correlate with individual susceptibility to toxicity and disease. Individual genetic differences harbored within the human population are believed to be the basis for individual susceptibility to environmental stressors including idiosyncratic drug toxicities. At present, environmental and drug safety assessment models use a very limited set of genetic models, which are insufficient to evaluate the influence of individual genetic differences on chemical and drug toxicity. The aim of this research and testing program is to model genetic diversity in the human population using genetically diverse laboratory animals. To meet this aim, the NTP is (1) planning, conducting, and analyzing research on chemical toxicity using multiple genetically defined and/or genetically modified animal models, and (2) developing the research base for internal and external research collaborations to promote investigations of the genetic basis for individual differences in susceptibility. By identifying the quantitative trait loci by haplotype-phenotype segregation analysis and conducting functional validation of candidate genes to identify allelic variants that modify individual response to chemical exposure and disease we can identify the key genes and pathways involved in responses to chemical exposures of presumed or known risk to humans. Using bioinformatics and comparative genetic analysis and identification of human orthologs, the NTP can aid extrapolation between animal models and human toxicity and disease.

The NTP has developed multi-disciplinary research projects to investigate individual differences in responses to environmental exposure to toxic agents and the associated development of complex polygenic diseases. The main aim of this research is to identify causally related genes and their variant isoforms in mouse models as surrogates for human exposure, and to develop predictive tools for genetic-based hazard identification and risk characterization.

Projects in progress during FY 2009:

- *ADME and Toxicogenetics*: Using benzene, which has been extensively studied in animals and humans, the NTP has tested multiple, genetically diverse, mouse inbred strains to determine the variable range of ADME kinetic parameters.
- *Environmental Cardiotoxins*: The NTP is developing a multi-strain mouse model to identify environmental cardiotoxins (compounds that cause damage to the heart muscle) and susceptibility to cardiotoxicity, using bis(2-chloroethoxy)methane, which has a metabolite in common with other known cardiotoxins. Heart disease is a leading cause of death in the United States, and this project will provide valuable insight into environmental exposure and heritable determinants to cardiotoxicity.
- *Aging, Environmental Exposures, and Disease*: The NTP has expanded research and testing of cancer models to include developing a benchmark reference database on aging and disease in 10 genetically diverse mouse inbred strains, for use in toxicology and carcinogenesis studies. Once the database has been used to develop and conduct short-term cancer bioassays with several inbred strains, the NTP will be prepared to perform pre-chronic and chronic multi-strain studies of toxicity and disease with nominated chemicals.

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Non-mammalian models – C. elegans

The NTP is currently evaluating *Caenorhabditis elegans* (*C. elegans*) as a study organism for assessing the effects of potential developmental and neurological toxicants on multi-cellular organisms. *C. elegans* is a roundworm about 1 mm in length that lives freely in soil and feeds on bacteria. The use of *C. elegans* is consistent with NTP's strategy to reduce the number of mammals used in testing. Several toxicology assays for feeding, growth, reproduction, and movement of *C. elegans* have been developed. In FY 2009 a *C. elegans* study was ongoing for bisphenol A.

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Biomolecular Screening

In 2008, the NTP established a high throughput screening (HTS) initiative, representing a new paradigm in toxicological testing. During 2009 the NTP continued using this HTS approach to screen for mechanistic targets active within cellular pathways critical to carcinogenicity, reproductive and developmental toxicity, genotoxicity, neurotoxicity, and immunotoxicity. The NTP's HTS program is administered through the Biomolecular Screening Branch (BSB).

The goals of the HTS Program are:

- To prioritize substances for further in-depth toxicological evaluation (to judiciously allocate efforts and resources to maximize public health impact)
- To identify mechanisms of action for further investigation (e.g., disease-associated pathways)
- To develop predictive models for biological responses in humans and animals (predictive toxicology)

Much of the research conducted in support of the HTS program is coordinated with the EPA and the National Human Genome Research Institute (NHGRI) through a Memorandum of Understanding (see page 82).
Contact Information: Dr. Raymond Tice, Chief BSB, *tice@niehs.nih.gov.* HTS website *http://ntp.niehs.nih.gov/go/28213.*

Toxicogenomics Studies

The NTP is working to bring the latest toxicogenomics technology into its testing program to help revolutionize the way NTP conducts its studies. Toxicogenomics examines how the entire genetic structure, or genome, is involved in an organism's response to environmental toxicants. It applies gene and protein technologies to environmental medicine by studying the effect of toxicants on gene activity and specific proteins produced by genes. This information could be useful to identify biomarkers of disease and exposure to toxic substances and for understanding individual genetic susceptibilities.

Preliminary toxicogenomic studies suggest that gene expression often is predictive for phenotypic alterations. The NTP is interested in determining if differential gene expression (DGE) analysis can provide indicators of toxicity at earlier time points and at lower doses than is possible with traditional toxicology parameters. DGE may provide more than a genotypic link to a morphology, because it is expected to provide insights into the pathogenesis of the disease and how different rodent models respond to toxicants.

Perhaps the most exciting potential of toxicogenomics is the possibility to identify biomarkers of exposure or biomarkers of effect. Changes that can be found in easily obtainable samples (blood, urine) could then be monitored in clinical studies. When the technology is validated, it will allow repeated sampling during long-term NTP studies to determine whether chemical exposures can be detected or whether developing cancers will provide a genetic signature.

The NTP is currently evaluating study conditions that may contribute to gene expression (e.g., animal and tissue variability), best methods of tissue sampling, and establishing standards for conducting toxicogenomic studies

under laboratory conditions. However, a long-term goal of the NTP is to find better and more accurate methods of predicting potential carcinogenicity, because current NTP carcinogenicity studies take four to five years to complete and are costly. Planned or ongoing NTP toxicogenomic studies are listed in Table 29.

Table 29: Toxicogenomics Studies (Planned or Ongoing)

Chemical	[CASRN]	Species/Strain	Study Route	Length	Project Leader
Aflatoxin B1	[1162-65-8]	Rats: F344/N	Feed	90 days	Irwin
Effect of the estrous cycle on hepatic transcriptome		Rats: Wistar Han	Not applicable	90 days	Irwin
Microcystin mixture	[101043-37-2] [96180-79-9]	Rats: F344/N	Intravenous	1/2/6/24 hrs	Walker
Microcystin – LR	[101043-37-2]	Rats: Wistar Han	Intravenous	1/2/6/24 hrs	Walker
Microcystin – LA	[96180-79-9]	Rats: F344/N	Intravenous	1/2/6/24 hrs	Walker
Evaluation of rat liver carcinogens and non-carcinogens administered by feed in: • Acetaminophen • Aflatoxin B1 • 1-Amino-2,4-dibromoanthraquinone • Ascorbic acid • Methyleugenol • *N*-nitrosodimethylamine • 1-Tryptophan	 [103-90-2] [1162-65-8] [81-49-2] [93-15-2] [50-81-7] [62-75-9] [73-22-3]	Rats: F344/N Tac	Feed Gavage Water	8 weeks 13 weeks	Irwin
Toxicogenomics study of allylbenzene and propenylbenzene class flavor constituents • Anethole • Estragole • Eugenol • soeugenol • Isosafrole • Methyleugenol • Myristicin • Safrole	 [104-46-1] [140-67-0] [97-53-0] [97-54-1] [120-58-1] [93-15-2] [607-91-0] [94-59-7]	Rats: F344/N Tac	Gavage	90 days	Irwin

Cellular and Molecular Pathology

Reproductive and Developmental Toxicity Study Pathology

The NTP sponsored the two-day Workshop on the Reproductive Tract on October 29-30, 2008, at the Biotechnology Center in Research Triangle Park, NC. The focus of the workshop was pathology of the male and female reproductive tracts in developing and mature rodents. Topics included gross pathology, physiology, male and female reproductive histology, histopathology, toxicology/organ toxicity, endocrine disruptors, and spermatogenesis. Input from this workshop has been used to redesign RACB studies (see page 67) to provide a more complete picture of the potential for agents to cause reproductive and developmental toxicity. NTP scientists Drs. Mark Cesta, David Malarkey, Darlene Dixon, and Susan Fenton are completing the NTP Reproductive and Developmental Toxicity Study Pathology Specifications, which will provide guidelines and address the specifics of study details and pathology review processes.

International Harmonization of Nomenclature and Diagnostic Criteria

NTP staff is playing a lead role in establishing the diagnostic criteria for non-neoplastic lesions in rats and mice by participating in the International Harmonization of Nomenclature and Diagnostic Criteria (INHAND) project. The INHAND Project is a joint initiative of the Societies of Toxicologic Pathology from Europe, Great Britain, Japan, and North America to develop an internationally accepted nomenclature for proliferative and nonproliferative lesions in laboratory animals. The first of a series of manuscripts on various organ systems is titled *Proliferative and nonproliferative lesions of the rat and mouse respiratory tract* (*Toxicol Pathol.* 2009;37(7 Suppl):5S-73S). The document provides a standardized nomenclature for classifying microscopic lesions observed in the respiratory tract. Extensive use of color photomicrographs provides examples of various lesions. The nomenclature is also available at *http://www.goreni.org/*. International harmonization of nomenclature for respiratory tract lesions in laboratory animals will decrease confusion among regulatory and scientific research organizations globally and provide a common language to enhance communication among toxicologists and pathologists. NTP contributors are Dr. Ronald Herbert and Dr. Amy Brix (on-site pathologist from Experimental Pathology Laboratories).

10th Annual NTP Satellite Symposium

The 10th Annual NTP Satellite Symposium was held on June 20, 2009, in conjunction with the Society of Toxicologic Pathology (STP) 28th Annual Meeting in Washington, DC. The NTP Satellite Symposium was conceived to present current diagnostic pathology issues to the toxicological pathology community. The theme for the 2009 symposium was Tumor Pathology, corresponding with the STP meeting's theme of cancer. The 2009 symposium, chaired by Dr. Susan Elmore, was one of the most highly attended interactive sessions of the STP. The symposium also included examples and discussion of INHAND nomenclature regarding neoplastic lesions. During each presentation, the speakers projected a series of lesion images on one screen with a choice of potential diagnostic choices listed on a separate screen. Members of the audience voted anonymously, and voting results were displayed as bar graphs with percentages on the screen. After each voting session, the speakers sometimes presented additional data to help decide on diagnosis or choice of terminology, and then time was allowed for discussion. Presentations by NTP staff included "*Kneejerks*" *welcomed: Diagnostic value of immunohistochemistry* by Dr. David Malarkey and *Hematopoietic cell proliferation versus myeloid hyperplasia*l by Dr. Greg Travlos. Proceedings of the symposium are in *Toxicologic Pathol.* 2010;38(1):9-36.

Molecular Mechanisms of Chemically Induced Neoplasia

NTP staff recently contributed to *A review of the molecular mechanisms of chemically induced neoplasia in rat and mouse models in National Toxicology Program bioassays and their relevance to human cancer (Toxicologic Pathol. 2009;37(7):835-48).* The review examined the underlying molecular mechanisms leading to carcinogenesis in animal models to evaluate their relevance to human health. Rodent tumors of the lung, colon, mammary gland, skin, and brain were examined for changes in cancer genes and epigenetic events associated with human cancer. NTP studies have identified several genetic alterations in chemically induced rodent neoplasms that are important in human cancer. Identifying such changes in rodent models of chemical carcinogenesis caused by exposure to environmental contaminants, occupational chemicals, and other compounds lends further support that they are of potential human health risk. These studies also emphasize the importance of molecular evaluation of chemically induced rodent tumors for providing greater public health significance for compounds evaluated by the NTP. NTP contributors were Drs. Mark Hoenerhoff, Hue Hua Hong, Tai-Vu Ton, Stephanie Lahousse, and Robert Sills.

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NTP Postdoctoral Training Programs

Toxicology and Carcinogenesis Training Program

Trainees in this program learn to perform all aspects of contracted toxicology studies for carcinogenic or non-carcinogenic endpoints (e.g., reproductive and developmental effects, immune system function). They learn about NTP efforts in molecular toxicology and HTS and receive training applicable to regulatory or industrial toxicology. By serving as study scientists in non-laboratory positions, they evaluate the toxicity of substances of interest to the NTP. They actively participate in designing, conducting, and evaluating studies and interact extensively with chemistry, pathology, toxicokinetics, toxicogenomics, genetics, epidemiology, statistics, and molecular biology staff. The three postdoctoral fellows previously in the program, Drs. Matt Stout, Scott Auerbach, and Chad Blystone, have all successfully moved on to full-time positions in the NTP, which held competitive national searches. After an extensive search during the summer of 2009, the postdoctoral training program recruited four talented new fellows: Drs. Minerva Mercado-Feliciano, In Ok Surh, Mamta Behl, and Sang-Hyun Kim.

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Laboratory Animal Medicine Training Program

This four-year training program includes clinical and surgical responsibilities, management of animal care facilities, participation in research projects, and laboratory animal pathology and is a collaborative effort between NIEHS and the University of North Carolina at Chapel Hill. Two postdoctoral fellows are currently in the program: Dr. Jacquelyn Tubbs, whose expected completion date is September 2010, and Dr. Coralie Zegre-Cannon, who will finish the program in September 2011. Fellows interact with laboratory animal veterinarians at NIEHS and at local area academic, industrial, and government facilities to receive didactic and hands-on training.

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Toxicological Pathology Training Program

Since formalizing the program in 2003, Dr. David Malarkey, training coordinator, and other Cellular and Molecular Pathology Branch staff have mentored 10 postdoctoral fellows and more than 20 veterinary student externs. Three postdoctoral fellows and seven veterinary students participated in the program during 2009. The program is designed to introduce students to the field and career opportunities in veterinary and toxicological pathology while also providing hands-on projects that often lead to abstracts and publications. Postdoctoral fellows learn rodent and toxicological pathology, participate in NTP and other research projects in the Division of Intramural Research, work to achieve accuracy of pathology data by assisting NTP pathologists in NTP studies, and continue education towards achieving board certification by the American College of Veterinary Pathologists (ACVP). During 2009, two fellows, Drs. Mike Boyle and Torrie Crabbs, passed the ACVP certifying exam and Dr. Deepa Rao achieved three of four sections. The NTP also hosted Dr. Koichi Yabe, a visiting Japanese pathologist, for one year.

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Interagency Agreements

NIEHS/NCTR Interagency Agreement

In 1992, the FDA entered into an IAG with NIEHS. The interagency agreement (IAG) is an instrument that allows chemicals nominated to the NTP to be studied for toxicity using the unique resources and facilities at NCTR. The research conducted under the IAG allows the FDA to better assess study design input and initial data on the safety of FDA-regulated products. The IAG allows continued collaborative toxicity testing on compounds of interest to the FDA and NTP and has led to investigations of mechanisms of action and assessments of toxicity for many classes of chemicals including cosmetics, endocrine-disrupting compounds, food contaminants, food cooking by-products, dietary supplements, drugs, and anesthetics. The IAG supports the Phototoxicity Research and Testing Laboratory at the NTP Center for Phototoxicology and the Nanotechnology Core Facility at the NCTR/ Office of Regulatory Affairs. All toxicology studies conducted under the IAG are designed with input from FDA regulatory scientists, NCTR and NIEHS scientists, scientists from other agencies, and invited subject matter experts. The IAG uses resources from public funds and exceptional scientific expertise to provide the best possible assessment of product safety through toxicological studies. Table 30 lists projects completed or ongoing in FY 2009.

Table 30: NIEHS/NCTR Interagency Agreement Projects FY 2009

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
para-Nonylphenol: Evaluation of Reproductive Effects over Multiple Generations [84852-15-3] *[Delclos]*	(1) To determine the effects of *p*-nonyphenol, an intermediate in the production of surfactants and other industrial products, on reproduction and on the development of reproductive and other hormone-sensitive organs when administered to CD rats over five generations; (2) to determine if subtle effects observed in the dose-range-finding study are magnified through multiple generations; and (3) to evaluate the reversibility of any observed effects.
Perinatal Carcinogenicity of Drug Combinations Used to Prevent Mother-to-Child Transmissions of HIV [30616-87-1], [134678-17-4] *[Beland]*	To determine the carcinogenicity, genotoxicity, and metabolism of antiretroviral drug combinations administered to mice transplacentally, perinatally, or neonatally.
Effect of Topically Applied Skin Creams Containing Retinyl Palmitate on the Photocarcinogenicity of Simulated Solar Light in SKH-1 Mice [79-81-2] *[Boudreau]*	(1) To study the effects of topically applied skin cream containing retinyl palmitate on the photocarcinogenicity of simulated solar light in SKH-1 mice and (2) to determine the mechanisms of tumor promotion by retinyl palmitate.
Bioassays in the F-344 Rat and B6C3F1 Mouse Administered *Aloe vera* Plant Constituents in Drinking Water [8001-97-6] *[Boudreau]*	To conduct bioassays in rats and mice using standardized preparations of *Aloe vera* to explore the limits of safety for the leaf constituents present in commercial products.
Toxicity Studies of a Combination of AIDS Drugs in p53 (+/-) Transgenic Mice [30616-87-1; 134678-17-4] *[Leakey]*	To evaluate the potential toxicity and carcinogenicity of perinatal and chronic exposures to the AIDS drugs zidovudine (AZT) and lamivudine in haplodeficient F1 transgenic mice.
Genotoxicity and Carcinogenicity of Acrylamide and Its Metabolite Glycidamide in Rodents [79-06-1; 5694-00-8] *[Beland]*	To compare the carcinogenicity of acrylamide and its metabolite glycidamide in B6C3F1 mice and F344 rats treated chronically for two years.
N-methyl-D-aspartic Acid (NMDA) Antagonist-/Gamma-aminobutyric Acid (GABA) Agonist-induced Cell Death in the Developing Rat Brain [1867-66-9] *[Wang, Slikker]*	To screen and evaluate pediatric anesthetic agents (NMDA antagonists/GABA agonists).
Developmental Neurotoxicity Assessment of Acrylamide in Rats: Long-term Studies [79-06-01] *[Paule]*	To determine the consequences of long-term exposure to acrylamide on a variety of developmental milestones and measures of nervous system integrity throughout life.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
Studies of Usnic Acid and Usnea Herb in Fischer 344 Rats and B6C3F1 Mice [125-46-2; 84696-53-7] *[Leakey]*	To establish appropriate doses of usnic acid and Usnea barbata preparations administered in feed to male and female Fischer 344 rats and B6C3F1 mice.
Subchronic Toxicity Studies of Chondroitin Sulfate and Glucosamine Combinations in Fischer 344 and Diabetic Goto-Kakizaki Rats [3416-24-8; 9007-28-7] *[Leakey]*	(1) To investigate the potential toxicity of chondroitin sulfate and glucosamine, administered by oral gavage in male rats, and (2) to determine whether subchronic exposure of glucosamine or chondroitin sulfate potentiates the pathological effects of noninsulin-dependent diabetes.
Toxicity Studies of Glucosamine and Glucosamine/Chondroitin Sulfate Combinations in Obese and Lean Zucker Rats [3416-24-8; 9007-28-7] *[Leakey]*	To investigate the potential toxicity of glucosamine and glucosamine/chondroitin sulfate combinations, administered by oral gavage in male rats.
DEHP Toxicokinetics in Neonatal Male Rhesus Monkeys after Intravenous and Oral Dosing [117-81-7] *[Delclos]*	(1) To quantify the metabolism and disposition of multiple, single-intravenous doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks, (2) to quantify the metabolism and disposition of multiple, single-oral doses of DEHP administered to male rhesus monkeys during the first 12 postnatal weeks, (3) to use the results of this work to evaluate the feasibility and utility of a subchronic toxicity study of DEHP, and (4) to utilize blood and testicular tissue from the infant monkeys to establish methods to be utilized in the subchronic study and/or estimate variability in the endpoints to aid in determining the number of animals that will be required in each dose group for a subchronic study.
The Immunogenicity of Permanent Makeup Inks and Their Components *[Howard]*	To determine the immunogenicity of permanent makeup inks using a modified lymph node proliferation assay protocol.
Effects of Sedatives on the Metabolism of DEHP Administered by Intravenous Injection and the Relationship of DEHP Metabolism to Biological Effects in Neonatal Rats [117-81-7] *[Delclos]*	(1) To determine if the metabolic profile of DEHP is affected by sedatives potentially useful for intravenous-injection studies of DEHP in neonatal rhesus monkeys and/or in common use in neonatal intensive care units and (2) to examine DEHP metabolism in neonatal rodents dosed intravenously and orally and relate this metabolism to biological effects.
Maintenance of the Transgenic p16/p19(-/-) Haplodeficient [NCTR strain code 7V] Breeding Colony *[Leakey]*	To provide support to maintain the p16/p19(-/-) breeding colony [NCTR code 7V] at NCTR for use in future NTP protocol development.
Determination of Carcinogenic Mechanisms for Furan in Male Fischer 344 Rats [110-00-9] *[Doerge]*	(1) To develop and validate liquid chromatography/electron spin tandem mass spectrometry (LC-ES/MS/MS) assays to quantify the major furan-derived DNA dducts in liver, the major furan-derived hemoglobin DNA adduct(s), and the major furan-derived urinary glutathione-derived metabolites; (2) to determine dose-response relationships for liver furan-derived DNA and hemoglobin adduct formation and repair/turnover of these adducts and the major furan-derived urinary glutathione-derived metabolites in male and female Fischer 344 rats following single and multiple dose exposures of rodents to furan; (3) to determine the concentration of furan in irradiated NIH-31 diet using headspace-GC/MS; (4) to determine the toxicokinetics of furan in male and female Fischer 344 rats following exposure by single gavage administration using headspace-GC/MS; (5) to combine all data to construct a physiologically based pharmacokinetic (PBPK) model for to determine carcinogenic risks to humans from exposure to furan through the diet; (6) to determine mutagenicity of furan in liver *in vivo* using male Big Blue© rats; (7) to determine dose-response relationships for furan-mediated hepatotoxicity and cell proliferation in livers of male and female Fischer 344 rats; and (8) to determine effects of furan on methylation status in rat liver and kidney DNA and histones as epigenetic changes related to carcinogenic process.
Subchronic Studies of Usnic Acid in Fischer 344 Rats and B6C3F1 Mice [125-56-2] *[Leakey]*	To evaluate the subchronic toxicity of usnic acid in male and female Fischer 344 rats and B6C3F1 mice.
Subchronic Studies of Usnea Lichen in Fischer 344 Rats and B6C3F1 Mice [84696-53-7] *[Leakey]*	To evaluate the subchronic hepatotoxicity of *Usnea* lichen in male and female Fischer 344 rats and B6C3F mice.

Study [CASRN] [Principal Investigator]	Objective and/or Rationale
Physiological Effects of Bitter Orange in Rats [94-07-5] *[Hansen]*	To determine potential physiological effects of synthetic synephrine as well as an extract from the botanical *Citrus aurantium* alone and combined with caffeine in rats with and without exercise.
Developmental Toxicity of Bitter Orange in Rats [94-07-5] *[Hansen]*	To determine potential developmental toxicity of synthetic synephrine and *Citrus aurantium* extract in rats.
Mechanisms of Nevirapine Carcinogenicity [129618-40-2] *[Beland]*	To determine the mechanism by which nevirapine induces liver tumors in rats.
A Toxicological Evaluation of Nanoscale Silver Particles in Rodents [7440-22-4] *[Boudreau]*	(1) To evaluate the effect of size of nanoscale silver particles on plasma protein binding in blood collected from adult rodents, using standard analysis methods to estimate the equilibrium association constant and maximum binding capacity; (2) to determine the effects of size and dose of nanoscale silver particles on their pharmacokinetic profiles and bioavailability, when administered orally and intravenously in rats, and whether they differ from those of silver acetate; and (3) to evaluate the absorption, biodistribution (including the potential to cross the blood-brain barrier), and excretion rates of nanoscale silver particles that differ in size.
Evaluation of the Toxicity of Bisphenol A (BPA) in Male and Female Sprague Dawley Rats Exposed Orally from Gestation Day 6 through Postnatal Day 90 [80-05-7] *[Delclos]*	To characterize the dose-response for orally administered BPA in the NCTR Sprague Dawley rat to examine effects in rodents near levels of exposure potentially experienced by humans.
Two-Year Carcinogenicity Bioassay of Furan in F344 Rats [110-00-9] [Beland]	To determine the dose-response relationship for the carcinogenicity of furan in F344 rats.
The Role of Perinatal Development on Toxicokinetics of BPA [80-05-7] *[Doerge]*	(1) To determine BPA pharmacokinetics at low doses; (2) to measure free and conjugated forms of BPA separately; (3) to use deuterium-labeled BPA to avoid issues of background contamination; (4) to use LC/MS/MS for sensitivity and selectivity of measurement; (5) to determine complete rat data sets for blood, tissue, and excreta across stages of development (pregnant females, fetuses, neonates); (6) to determine BPA pharmacokinetics from oral and intravenous administration in pregnant, lactating, and nonpregnant female rats and neonatal rats; (7) to determine plasma and urinary pharmacokinetic data in neonatal and adult monkeys; and (8) to use the new pharmacokinetic data in conjunction with literature data from experimental animals and humans to build a PBPK model for BPA.
Assessment of the Nephrotoxic Effect of a Combined Exposure to Melamine and Cyanuric Acid [108-78-1; 64-18-6] *[Gamboa Da Costa]*	(1) To conduct a pharmacokinetic study on the absorption and disposition of melamine and cyanuric acid in F344/N rats when administered individually by gavage, simultaneously as a separate base and acid, and simultaneously as a pre-formed salt; (2) to determine the NOAEL of combined exposure to melamine and cyanuric acid in F344/N rats for 28 and 90 days; (3) to investigate the occurrence of early metabonomic and proteomic biomarkers of nephrotoxicity induced by melamine + cyanuric acid that are obtainable by noninvasive methods; and (4) to investigate the pharmacokinetics and determine the NOAEL of a combined exposure to melamine plus cyanuric acid in a mini-pig model considered representative of the human kidney's anatomy and physiology.

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NIEHS/NIOSH Interagency Agreement – Comprehensive Assessment of Occupationally-Relevant Exposures

The NTP is coordinating an effort with NIOSH to better understand worker exposures, identify occupational health research gaps, and educate workers. Current efforts listed in Table 31 address worker exposure to welding fumes, abrasive blasting materials, metalworking fluids, tungsten oxide fibers, and nano-sized materials.

Table 31: NIEHS/NIOSH Interagency Agreement on Occupationally Relevant Exposures

Task Order [Project Officer]	Objective and/or Rationale
Administrative Support *[Toraason]*	To enable NIOSH scientists to (1) participate in review and oversight of NTP activities and (2) attend NTP-related meetings in Research Triangle Park, NC and Washington, DC.
Tungsten Oxide Fiber Dissolution and Persistence in Artificial Human Lung Fluids *[Stefaniak]*	To characterize the physicochemical properties and dissolution behaviors of fiber-containing tungsten oxide materials in artificial lung fluids to determine their relative biopersistence.
Assessing the Feasibility of Industry-wide Exposure and Epidemiology Studies of Engineered Nanomaterials *[Schubauer-Berigan]*	(1) To collect and compile information on the size, characteristics, and future trends of the U.S. workforce involved in the manufacture of engineered carbonaceous nanomaterials, and (2) to develop a report on the feasibility of conducting industry-wide exposure surveys and epidemiologic studies among this workforce.
Assess the Feasibility of an Occupational Exposure Assessment of Welding Fumes with Emphasis on Manganese Compounds *[Hanley]*	(1) To identify industries (e.g., construction, shipbuilding, railroad, and manufacturing), companies, and/or unions involved in welding operations where the potential for substantial manganese exposure exists for exposure assessments; (2) to develop methods to identify specific manganese compounds, different valence states, and potential solubility contained within various welding fumes matrices; and (3) to characterize welding fume exposures based on welding-associated jobs, tasks, and processes.
Exposure Assessment of Diacetyl and Other Flavorings in Food Production Industries *[Curwin]*	(1) To characterize workplace inhalation exposures to diacetyl in food production industries that use food flavorings, (2) to document high-exposure activities and processes in flavored food production industries, (3) to identify work practices and procedures that affect exposure, (4) to document engineering controls, and (5) to field test novel techniques for both gravimetric and volatile sampling.
Exposure Assessment of Dithiobisbenzanilide (DTBBA) in a Manufacturing Setting *[Wurzelbacher]*	(1) To identify worker populations at increased risk of inhalation and surface exposure to DTBBA during a manufacturing process, (2) to develop a NIOSH analytical method for quantitatively assessing DTBBA airborne particulate and surface exposures, and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to DTBBA.
Assessment of Use of Indium and Indium Compounds in the Workplace *[Hines]*	(1) To contact and visit companies to determine indium materials being used, jobs and processes with potential indium exposure, exposure controls, and indium use trends; (2) to attend the Semiconductor Environmental Safety and Health Association meeting to establish contacts in industry and other organizations involved in indium-related applications; and (3) to conduct preliminary sampling for indium, if possible.
Exposure Assessment of Engineered Nanoparticles *[Geraci]*	(1) To identify workplaces engaged in the synthesis, manufacture, and use of engineered nanomaterials, and (2) to characterize workplace exposure to selected engineered nanoparticles.
Exposure Assessment of 1-Chloro-4-(trifluoromethyl) benzene (PCBTF) *[Harper]*	(1) To identify worker populations at elevated risk of inhalation and surface exposure to PCBTF during manufacturing processes, (2) to update a previously published analytical method for quantitatively assessing PCBTF airborne vapors and surface exposures to allow the use of capillary column chromatography, and (3) to characterize industry wide occupational exposures, including total number of workers, and evaluate patterns of exposure to PCBTF.
Exposure Assessment of Ethylene glycol 2-ethylhexyl ether (EGEHE) *[Harper]*	(1) To identify worker populations at increased risk of inhalation and surface exposure to EGEHE during manufacturing processes, (2) to develop a sampling and analytical method for quantitatively assessing EGEHE airborne vapors and aerosols and surface exposures, and (3) to characterize industry-wide occupational exposures, including total number of workers, and evaluate patterns of exposure to EGEHE.
Cardiovascular Toxicity Assessment of Subchronic Inhalation Exposure to Fullerene C60 *[Erdely]*	(1) To evaluate potential cardiovascular toxicity of fullerene C60 in animal models using molecular and biochemical analysis of cardiovascular tissue and blood samples from NTP inhalation studies, and (2) to correlate the findings with the results from histopathology, particle distribution, and blood chemistry studies.

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NIEHS/NIOSH Interagency Agreement – Immunotoxicology

The goal of this IAG is to provide support of NTP hazard identification activities aimed at preventing diseases or adverse effects caused by environmental exposure to chemical or physical agents. These cooperative studies continue to improve risk assessment by measuring what constitutes an adverse health effect on the immune system in humans. The studies, listed in Table 32, evaluate unique cohorts of individuals from professions associated with immune-mediated occupational diseases, including asthma, contact dermatitis, allergy to mold spores, chronic beryllium disease, allergic rhinitis, silicosis, and latex allergy. These cohorts are being studied for a number of endpoints including impact of genetic polymorphisms on development of inflammatory disease and clinical outcomes, and identification of unique immunological biomarkers for disease. The NIOSH Laboratory for Occupational Genomics serves as a resource for obtaining samples from individuals with occupational and occupationally related diseases.

Table 32: NIEHS/NIOSH Interagency Agreement on Immunotoxicology Studies, FY 2009

Study [Principal Investigator]	Objective and/or Rationale
Chronic Sinusitis and Mold Exposure *[Beezhold]*	To investigate the role of fungi in chronic sinusitus (1) to determine the prevalence of sensitization to a panel of seasonal allergens in chronic rhinosinusitis patients, and (2) to determine if the prevalence of fungal sensitization is different from that to seasonal allergens in chronic rhinosinusitis patients.
Heading off Environmental Asthma in Louisiana *[Beezhold]*	(1) To evaluate the effectiveness of a novel asthma case management intervention among children with asthma after Hurricane Katrina in New Orleans, and (2) to assess total immunoglobulin E (IgE) and mold-specific IgE in asthmatic children before and after the intervention. This study is in collaboration with Tulane University.
NIEHS Agricultural Pesticide Study *[Beezhold]*	(1) To evaluate allergic sensitization in a cohort of sera from 700 farmers with or without pesticide exposures, and (2) to measure levels of deoxinivinol (a potential biomarker for occupational exposures) in the serum.
Role of Genetic Variation in Environmental and Occupational Diseases – Irritant Dermatitis Genetics *[Yucesoy]*	(1) To test the hypothesis that individuals with increased susceptibility to occupational irritants express a certain genetic pattern and that this pattern is associated with polymorphisms in genes that control immune and inflammatory responses, and (2) to support purchase of gene platforms and fund research collaborators for subject compensation. This study is in collaboration with Case Western Reserve University and West Virginia University School of Medicine.
Role of Genetic Variation in Environmental and Occupational Diseases – Occupational Asthma *[Yucesoy]*	(1) To investigate the association between functional polymorphisms within cytokine, inflammatory, antioxidant, and major histocompatibility complex genes and the occurrence and clinical outcomes of asthma, gene-gene/gene-environment interactions, and (2) to study single nucleotide polymorphisms in the major histocompatibility complex region.
Investigations into Health Effects Caused by Exposure to Indoor Air Reaction Products (supportive animal studies) *[Wells, Anderson]*	(1) To identify and measure the reaction products of gas-phase compounds present in the indoor environment, especially dicarbonyls; (2) to investigate the immunotoxic effects of these reaction products; (3) to identify biomarkers that can be used to screen indoor environments; and (4) to complete both *in vitro* and *in vivo* assays to assess adverse health effects caused by exposure to indoor air reaction products.
Immunological Mechanisms of Occupational Rhinitis Induced by Diisocyanate Exposure (supportive animal studies and field studies) *[Johnson]*	(1) To diagnose and collect samples from workers from Canada and Spain exposed to diisocyanates; (2) to clinically characterize upper and lower airway disease, as well as specific inhalation challenge with the suspected diisocyanate compound; and (3) to gain an understanding of the pathobiology of occupational rhinitis that may help identify biomarkers useful in earlier diagnosis of disease.
Toluene Diisocyanate (TDI) Monoclonal Antibody Production and Characterization (improved methods) *[Siegel]*	(1) To produce and characterize 35 monoclonal antibodies against 2,4-TDI protein and 13 monoclonal antibodies against 2,6-TDI-protein; (2) to complete characterization of all monoclonal antibodies, especially with respect to minimal epitope required for reactivity of the monoclonal antibodies to a TDI-reacted chemical; and (3) to examine the utility of select monoclonal antibodies for immunoassay, immunohistochemistry, and proteomic analyses of tissues after TDI exposure.
Determination of Total IgE, Antinuclear Antibodies and Atopy In Plasma From Members of Upper Midwest Health Study, A Case-Control Study of Intracranial Gliomas (field study) *[Biagini]*	To assess members of the Upper Midwest Health Study (1) to determine total IgE, antinuclear antibodies, and atopy in plasma, and (2) to test for common allergies.
Antibody Levels in Systemic Lupus Erythematosus (field study) *[Biagini]*	To measure total serum IgA, IgM and IgG in sera from systemic lupus erythematosus patients to investigate whether adjustment for total immunoglobulin levels may unmask differences in serum IgE levels.

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NTP/NHGRI/EPA Interagency Agreement – High Throughput Screening, Toxicity Pathway Profiling, and Biological Interpretation of Findings

A five-year Memorandum of Understanding (MOU), *High Throughput Screening, Toxicity Pathway Profiling and Biological Interpretation of Findings*, was signed on February 14, 2008. With this MOU, NTP is partnering with the National Human Genome Research Institute's (NHGRI) NIH Chemical Genomics Center (NCGC) and the U.S. EPA's National Center for Computational Toxicology located within the Office of Research and Development. A central component of this MOU is the exploration of quantitative high throughput screens (qHTS) and tests using phylogenetically lower animal species (e.g., fish, worms), as well as high throughput whole-genome analytical methods, to evaluate mechanisms of toxicity. Ultimately, the data generated by these new tools will be provided to risk assessors to use to protect human health and the environment.

The goals of this MOU are to investigate the use of these new tools to (1) identify mechanisms of chemically induced biological activity, (2) prioritize chemicals for more extensive toxicological evaluation, and (3) develop more predictive models of *in vivo* biological response. The results should yield test methods for toxicity testing that are more scientifically and economically efficient and models for risk assessment that are more biologically based. This should reduce or replace animals in regulatory testing and is anticipated to occur in parallel with an increase in our ability to evaluate the large numbers of chemicals that currently lack adequate toxicological evaluation. Through this partnership, it is possible to pool resources, overcome the resource limitations of a single agency, build on existing expertise, and avoid the need to create a new administrative and support structure.

By the end of FY 2009, a library of approximately 2,800 compounds provided to the NCGC for qHTS by the NTP and the EPA had been tested in the following areas and assays:

Apoptosis

- Caspase-Glo® assays for caspases 3/7 (13 cell types) and 8 or 9 (6 cell types each)

Cell Viability

- CellTiter-Glo® luminescent cell viability assay (13 cell types - 9 human, 4 rodent)
- Cytotox-ONE™ homogeneous membrane integrity assay and a proteolytic release assay (both in two cell types)

Epigenetics

- A locus derepression assay in murine cells to detect compounds that act as histone deacetylase or DNA methyltransferase inhibitors

Genotoxicity

- Differential cytotoxicity in chicken lymphoblastoid cell lines deficient in different DNA repair pathways (wild-type plus seven repair-deficient clones)
- P53 signaling pathway in HCT-116 colon epithelial cells

Nuclear Receptors (tested in agonist and antagonist mode)

- Human androgen receptor (hAR) in HEK 293 human embryonic kidney cells
- Human ER α in HEK 293 cells
- Human farnesoid X receptor (FXR) in HEK 293 cells
- Human glucocorticoid receptor (hGR) in HeLa cells
- Human liver X receptor β (hLXRβ) in HEK 293 cells
- Human peroxisome proliferator-activated receptor δ (hPPARδ) in HEK 293 cells
- Human peroxisome proliferator-activated receptor γ (hPPARγ) in HEK 293 cells

- Human pregnane X receptor (hPXR) in HepG2 human liver carcinoma cells
- Rat pregnane X receptor (rPXR) in HepG2 cells
- Human retinoid X receptor (hRXR) in HEK 293 cells
- Human thyroid hormone receptor β (hTRβ) in HEK 293 cells
- Human vitamin D receptor (hVDR) in HEK 293 cells

Stress Response Pathways

- Antioxidant response element (ARE) signaling pathway in HepG2 cells
- Hypoxia response element (HRE) in ME-180 human cervical carcinoma cells
- Heat shock protein (HSP) response in HepG2 cells

Other Assays

- Activator protein-1 (AP-1) in ME-180 cells
- Nuclear factor kappa B (NFκB) in ME-180 cells
- Mitochondrial toxicity

In addition, efforts to evaluate differential sensitivity among lymphoblastoid cells from humans continued by exposing ~80 HapMap cell lines to 240 toxic chemicals and evaluating the extent of cytotoxicity and induction of caspase 3/7 across different cell lines.

During 2009, the partners established a library of ~10,000 compounds that broadly characterizes and defines the chemical-biological space occupied by chemicals of toxicological concern. This library, to be completed by mid-2010, will be tested at the NCGC with qHTS and quantitative high content screens (qHCS) that provide information on critical cellular pathways. The identity, purity, and stability of all compounds in this library will be determined. A subset of these compounds (~700) will be tested in Phase II of EPA's ToxCast™ Program (*http://www.epa.gov/ncct/toxcast/*). The data from these assays, along with full chemical characterization and assay protocol details, are being deposited into publicly accessible, relational databases such as the National Library of Medicine's PubChem (http://pubchem.ncbi.nlm.nih.gov/), EPA's ACToR (*http://www.epa.gov/ACToR/*) and NTP's CEBS (*http://www.niehs.nih.gov/research/resources/databases/cebs/*). Secondary screens using the *C. elegans* model (*http://www.niehs.nih.gov/research/atniehs/labs/bmsb/index.cfm*) are being developed. The tripartite collaboration between NTP, EPA, and NCGC will establish a full spectrum of secondary and tertiary screening assays to further define and characterize activities identified in initial qHTS and qHCS.

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NIEHS/EPA Interagency Agreement – The Phthalate Initiative

Di(2-ethyl)hexyl phthalate (DEHP) and other phthalates have been nominated to the NTP for testing. To address these nominations, the NIEHS and EPA signed *The Phthalate Initiative* IAG in June 2008, which was renewed in July 2009. Many aspects of this IAG would fall under nominations previously approved by the BSC for the study of peroxisome proliferators (begun in the 1990s), the nomination of DEHP by the FDA in 2004, and the critical data need highlighted in the NTP Monograph on DEHP issued in 2006.

These studies will clarify how the peroxisome proliferator-activated receptor alpha (PPARα) develops in the rat and its relationship to DEHP-related cancer and other developmental toxicities. The studies will also provide critical data for future mixture studies using various models to inform on potential risks for toxicity over time and during development. Recent data have indicated that because phthalate esters have similar modes of action *in utero*, they show dose-addition when administered in combination; therefore, it would be appropriate to consider cumulative risk for the class, since human subjects (including fetuses) are typically exposed to multiple phthalates.

The initiative has two specific aims:

(1) Undertake an ontogeny study of PPARα in the rat to determine when the receptor is first expressed in target tissues. This study will test the hypothesis that PPARα is developmentally regulated in the rat and unlikely to contribute to toxicity initiated *in utero* after exposure to DEHP.

(2) Undertake perinatal phthalate mixture studies. These studies will test the hypothesis that exposures to mixtures of phthalates, based on their individual potencies, would result in dose-addition for cancer (and potentially other) outcomes.

Based on data generated in 2009, a short-term *in utero* screen has been developed to evaluate individual phthalates and mixtures in the Harlan Sprague Dawley rat. This model is also appropriate for studying developmental effects of various phthalates. Phthalates' ability to alter fetal testicular testosterone production, induce changes in specific fetal testicular genes (especially related to steroidogenesis and testicular descent), and the induction of specific male reproductive tract malformations that have been termed the "phthalate syndrome." These data would guide selection of individual studies to investigate potential short-term biomarkers for toxicity, which in turn would support future perinatal bioassays and phthalate mixture work. The NTP has now designed both perinatal and standard bioassays to evaluate developmental and cancer potential from different exposure paradigms, which should begin in early 2010. This information will be extremely valuable in assessing potential cumulative risk of phthalates, as has been advocated by a recent National Academy of Sciences committee report, and efforts by EPA's Integrated Risk Information System (IRIS) program.

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NTP FY 2009 Bibliography

Ali AA, Lewis SM, Badgley HL, Allaben WT, Frankos VH and Leakey JE. 2009. Potential toxicity of glucosamine mediated through transforming growth factor beta. *J Amer Assoc for Lab Animal Sci* 48(5):635-636.

Anderson SE, Brown KK, Butterworth LF, Fedorowicz A, Jackson LG, Frasch HF, Beezhold D, Munson AE, Meade BJ. 2009. Evaluation of irritancy and sensitization potential of metalworking fluid mixtures and components. *J Immunotoxicol* 6(1):19-29.

Antonini JM, Roberts JR, Stone S, Chen BT, Schwegler-Berry D and Frazer DG. 2009. Short-term inhalation exposure to mild steel welding fume had no effect on lung inflammation and injury but did alter defense responses to bacteria in rats. *Inhal Toxicol* 21(3):182-92.

Antonini JM, Sriram K, Benkovic SA, Roberts JR, Stone S, Chen BT, Schwegler-Berry D, Jefferson AM, Billig BK, Felton CM, Hammer MA, Ma F, Frazer DG, O'Callaghan JP and Miller DB. 2009. Mild steel welding fume causes manganese accumulation and subtle neuroinflammatory changes but not overt neuronal damage in discrete brain regions of rats after short-term inhalation exposure. *Neurotoxicol* 30(6):915-25.

Apopa PL, Qian Y, Shao R, Guo NL, Schwegler-Berry D, Pacurari M, Porter D, Shi X, Vallyathan V, Castranova V and Flynn DC. 2009. Iron oxide nanoparticles induce human microvascular endothelial cell permeability through reactive oxygen species production and microtubule remodeling. *Part Fibre Toxicol* 6:1. epub.

Antunes AMM, Godinho A, Marques MM, Martins I and Beland FA. 2009. Protein adduct formation by the nevirapine metabolite, 12-hydroxynevirapine-A possible factor in nevirapine toxicity. *Toxicol Lett* 189:S103-S103.

Arias H, Santamaria A, and Ali SF. 2009. Pharmacological and neurotoxicological actions mediated by bupropion and diethylpropion. *Intl Rev Neurbiol* 88:223-239.

Ashley K, McKernan LT, Burroughs E, Deddens J, Pendergrass S, Barbero AM, Frasch HF. 2009. Pig and guinea pig skin as surrogates for human *in vitro* penetration studies: a quantitative review. *Toxicol* In Vitro 23(1):1-13.

Auerbach SS, Mahler J, Travlos GS and Irwin RD. 2008. A comparative 90-day toxicity study of allyl acetate, allyl alcohol and acrolein. *Toxicol* 253(1-3):79-88.

Baek S, Kweon O, Kim S, Baek D, Chen JJ, Cerniglia CE 2009. ClassRHO: A platform for classification of bacterial rieske non-heme iron ring-hydroxylating oxygenases. *J Microbiol Meth* 76(3):307-309.

Beger R, Hansen DK, Schnackenberg L, Cross BM, Fatollahi JJ, Lagunero FT, Sarnyai Z, Boros LG. 2009. Single valproic acid treatment inhibits glycogen and RNA ribose turnover while disrupting glucose-derived cholesterol synthesis in liver as revealed by the [U-13C6]-D-glucose tracer in mice. *Metabolomics* 5:336-345.

Beilke LD, Aleksunes LM, Holland RD, Besselsen DG, Beger R, Klaassen CD, Cherrington NJ. 2009. Car-mediated changes in bile acid composition contributes to hepatoprotection from LCA-induced liver injury in mice. *Drug Metab Disp* 37(5):1035-1045.

Beseler CL, Stallones L, Hoppin JA, Alavanja MCR, Blair A, Keefe T and Kamel F. 2008. Depression and pesticide exposures among private pesticide applicators enrolled in the agricultural health study. *Environ Health Perspect* 116(12):1713-1719.

Baird DD, Travlos G, Wilson R, Dunson DB, Hill MC, D'Aloisio AA, London SJ and Schectman JM. 2009. Uterine leiomyomata in relation to insulin-like growth factor-I, insulin, and diabetes. *Epidemiol* 20(4):604-10.

Barbero AM, Frasch HF. 2009. Pig and guinea pig skin as surrogates for human *in vitro* penetration studies: A quantitative review. *Toxicol* in Vitro 23(1):1-13.

Barter ZE, Chowdry JE, Harlow JR, Snawder JE, Lipscomb JC, Rostami Hodjegan A. 2008. Covariation of human microsomal protein per gram of liver with age: absence of influence of operator and sample storage may justify interlaboratory data pooling. *Drug Metab Disp* 36(12):2405-2409.

Beger RD, Hansen DK, Schnackenberg LK, Cross BM, Fatollahi JJ, Lagunero FT, Sarnyai Z and Boros LG. 2009. Single valproic acid treatment inhibits glycogen and RNA ribose turnover while disrupting glucose-derived cholesterol synthesis in liver as revealed by the [U-C-13(6)]-d-glucose tracer in mice. *Metabolomics* 5(3):336-345.

Benkovic SA, O'Callaghan JP, Miller DB. 2009. Protracted exposure to supraphysiological levels of corticosterone does not cause neuronal loss or damage and protects against kainic acid-induced neurotoxicity in the hippocampus of C57BL/6J mice. *Neurotoxicol* 30(6):965-976.

Beseler CL, Stallones L, Hoppin JA, Alavanja MCR, Blair A, Keefe T, Kamel F. 2008. Depression and pesticide exposures among private pesticide applicators enrolled in the agricultural health study. *Environ Health Perspect* 116(12):1713-1719.

Bienek DR, Loomis LJ and Biagini RE. 2009. The anthrax vaccine No new tricks for an old dog. *Human Vaccines* 5(3):184-189.

Birnbaum LS. 2009. Leading the world's premier environmental health organization: A message from Linda Birnbaum. *Environ Health Perspect* 117(4): A138-A138.

Bishop JB, Wassom JS. 2009. The next 50 years in germ cell mutagenesis research. *Environ Molec Mut* 50(7): 537-537.

Blachere FM, Lindsley WG, Pearce TA, Anderson SE, Fisher M, Khakoo R, Meade BJ, Lander O, Davis S, Thewlis RE, Celik I, Chen BT, Beezhold DH. 2009. Measurement of airborne influenza virus in a hospital emergency department. *Clin Infect Dis* 48(4):438-440.

Boctor SY, Ferguson SA. 2009. Altered adult locomotor activity in rats from phencyclidine treatment on postnatal days 7,9, and 11, but not repeated ketamine treatment on postnatal day 7. *Neurotoxicol* 31(1):42-54.

Boctor SY, Ferguson SA. 2009. Neonatal NMDA receptor antagonist treatments have no effects on prepulse inhibition of postnatal day 25 Sprague Dawley rats. *Neurotoxicol* 30(1):151-154.

Boctor S, Wang C, Ferguson SA. 2009. Neonatal PCP is more potent than ketamine at modifying preweaning behaviors of Sprague Dawley rats. *Neurotoxicol Teratol* 31(4):NBTS42.

Boedigheimer MJ, Chou JW, Corton JC, Fostel J, O'Lone R, Pine PS, Quackenbush J, Thompson KL, Wolfinger RD 2009. Variance due to smooth bias in rat liver and kidney baseline gene expression in a large multi-laboratory data set. In Batch Effect and Noise in Microarry Experiments: *Sources and Solutions*. 87-100.

Boyd WA, Smith MV, Kissling GE, Freedman JH. 2009. Medium-and high throughputscreening of neurotoxicants using *C.elegans*. *Neurotoxicol Teratol* 32:68-73.

Bowyer JF, Latendresse JR, Delongchamp RR, Warbritton AR, Thomas M, Divine B, Doerge DR. 2009. The mRNA expression and histological integrity in rat forebrain motor and sensory regions are minimally affected by acrylamide exposure through drinking water. *Toxicol Appl Pharmacol* 240(3):401-411.

Boyd WA, Smith MV, Kissling GE, Rice JR, Snyder DW, Portier CJ, Freedman JH. 2009. Application of a mathematical model to describe the effects of chlorpyrifos on *Caenorhabditis elegans* development. *PLoS One* 4(9):e7024.

Bradman A, Salvatore AL, Boeniger M, Castorina R, Snyder J, Barr DB, Jewell NP, Kavanagh Baird G, Striley C, Eskenazi B. 2009. Community-based intervention to reduce pesticide exposure to farmworkers and potential take-home exposure to their families. *J Expo Sci Environ Epidemiol* 19(1):79-89.

Bucher JR. 2009. Bisphenol A: Where to now? *Environ Health Perspect* 117(3):A96-A97.

Bushel, P.R., Nielsen, D., and Tong, W. 2009. Proceedings of the First International Conference on Toxicogenomics Integrated with Environmental Sciences (TIES-2007). *BMC Proceedings*. 3(Suppl 2):S1.

Cao Y, Calafat AM, Doerge DR, Umbach DM, Bernbaum JC, Twaddle NC, Ye XY, Rogan WJ. 2009. Isoflavones in urine, saliva, and blood of infants: data from a pilot study on the estrogenic activity of soy formula. *J Exposure Sci Environ Epidemiol* 19(2):223-234.

Cesta MF, Ryman-Rasmussen JP, Wallace DG, Masinde T, Hurlburt G, Taylor AJ, Bonner JC. 2009. Bacterial lipopolysaccharide enhances PDGF signaling and pulmonary fibrosis in rats exposed to carbon nanotubes. *Am J Respir Cell Mol Biol*. [epub ahead of print].

Chamberlain PL, Cerniglia CE, Mclean J. Narasin. 70th Joint FAO/WHO Expert Committee on Food Additives.

Chang QS, Chen JG, Beezhold KJ, Castranova V, Shi XL, Chen F. 2009. JNK1 activation predicts the prognostic outcome of the human hepatocellular carcinoma. *Molec Cancer* 8:64.

Chang MH, Lindegren ML, Butler MA, Chanock SJ, Dowling NF, Gallagher M, Moonesinghe R, Moore CA, Ned RM, Reichler MR, Sanders CL, Welch R, Yesupriya A, Khoury MJ. 2009. Prevalence in the United States of selected candidate gene variants. *Am J Epidemiol* 169(1):54-66.

Chang QS, Zhang YD, Beezhold KJ, Bhatia D, Zhao HW, Chen JG, Castranova V, Shi XL, Chen F. 2009. Sustained JNK1 activation is associated with altered histone H3 methylations in human liver cancer. *J Hepatol* 50(2):323-333.

Cheever KL, Marlow KL, B'Hymer C, Hanley KW, Lynch DW. 2009. Development of an HPLC-MS procedure for the quantification of *N*-acetyl-S-(*n*-propyl)-l-cysteine, the major urinary metabolite of 1-bromopropane in human urine. *J Chromatogr B Analyt Technol Biomed Life Sci* 877(8-9):827-32.

Chen B. 2009. New Centers for Disease Control and Prevention publication on good laboratory practices for molecular genetics testing. *Beijing Da Xue Xue Bao* 41(4):395-396.

Chen B, Gagnon M, Shahangian S, Anderson NL, Howerton DA, Boone JD. 2009. Good laboratory practices for molecular genetic testing for heritable diseases and conditions. *MMWR Recomm Rep* 58(RR-6):1-37; quiz CE-1-4.

Chen F, Beezhold K, Castranova V. 2009. JNK1, a potential therapeutic target for hepatocellular carcinoma. *Biochim Biophys Acta* 1796(2):242-51.

Chen F, Castranova V. 2009. Beyond apoptosis of JNK1 in liver cancer. *Cell Cycle* 8(8):1145-1147.

Chen G, Bower KA, Xu M, Ding M, Shi XL, Ke ZJ, Luo J. 2009. Cyanidin-3-glucoside reverses ethanol-induced inhibition of neurite outgrowth: Role of glycogen synthase kinase 3 beta. *Neurotoxicol Res* 15(4):321-331.

Chen H, Xu H, Heinze TM, Cerniglia CE. 2009. Decolorization of water and oil-soluble azo dyes by Lactobacillus acidophilus and Lactobacillus fermentum. *J Ind Microbiol Biotech 36*(12):1459-66.

Chen HF, Su PH, Zhu YM. 2009. Morphology determination of multi-needle bipolar corona discharge by OES. Guang Pu Xue Yu Guang Pu Fen Xi/*Spectroscopy Spectral Anal* 29(1):24-27.

Chen T, Heflich RH, Moore MM and Mei N. 2009. Differential mutagenicity of aflatoxin B(1) in the liver of neonatal and adult mice. *Environ Mol Mutagen* 51(2):156-63.

Cheng Y, Wright SH, Hooth MJ and Sipes IG. 2009. Characterization of the disposition and toxicokinetics of *n*-butylpyridinium chloride in male F-344 rats and female B6C3F1 mice and its transport by organic cation transporter 2. *Drug Metabol Dispos* 37(4):909-916.

Chipinda I, Anderson SE, Butterworth LF, Beezhold D and Siegel PD. 2009. Increased cell proliferation in spleen and lymph nodes peripheral to contact allergen application site. *Toxicol* 257(3):113-6.

Cleveland BM, Leonard SS, Klandorf H, Blemings KP. 2009. Urate oxidase knockdown decreases oxidative stress in a murine hepatic cell line. *Oxidat Med Cell Longev* 2(2):93-98.

Cohen SM, Storer RD, Criswell KA, Doerrer NG, Dellarco VL, Pegg, DG Wojcinski, ZW Malarkey, DE Jacobs, AC Klaunig JE, Swenberg JA, Cook JC. 2009. Hemangiosarcoma in rodents: Mode-of-action evaluation and human relevance. *Toxicol Sci* 111(1):4-18.

Cui Y and Freedman JH. 2009. Cadmium induces retinoic acid signaling by regulating retinoic acid metabolic gene expression. *J Biol Chem* 284(37):24925-24932.

Cullen JM, Brown DL, Kissling GE, Foley JF, Rizzo J, Marion PL, Parron VI, French, JE. 2009. Aflatoxin B1 and/or hepatitis B virus Induced tumor spectrum in a genetically engineered hepatitis B virus expression and Trp53 haploinsufficient mouse model system for hepatocarcinogenesis. *Toxicol Pathol* 37(3):333-342.

Curwin BD, Hein MJ, Barr DB, Striley C. 2009. Comparison of immunoassay and HPLC-MS/MS used to measure urinary metabolites of atrazine, metolachlor, and chlorpyrifos from farmers and non-farmers in Iowa. *J Expo Sci Environ Epidemiol* 20(2):205-212.

Dabkowski ER, Williamson CL, Bukowski VC, Chapman RS, Leonard SS, Peer CJ, Callery PS, Hollander JM. 2009. Diabetic cardiomyopathy-associated dysfunction in spatially distinct mitochondrial subpopulations. *Am J Physiol Heart Circ Physiol* 296(2):H359-H369.

D'Aloisio AA, Schroeder JC, North KE, Poole C, West SL, Travlos GS, Baird DD. 2009. IGF-I and IGFBP-3 polymorphisms in relation to circulating levels among African American and Caucasian women. *Cancer Epidemiol Biomarkers Prev* 18(3):954-966.

DeKeyser JG, Stagliano MC, Auerbach SS, Prabhu KS, Jones AD, Omiecinski CJ. 2009. Di(2-ethylhexyl) phthalate Is a highly potent agonist for the human constitutive androstane receptor splice variant CAR2. *Mol Pharm* 75(5):1005-1013.

Delclos KB , Weis CC, Bucci TJ, Olson GR, Mellick PW, Sadovova, NV, Latendresse JR, Thorn BT, Newbold R. 2009. Overlapping but distinct effects of genistein and ethinyl estradiol (EE(2)) in female Sprague Dawley rats in multigenerational reproductive and chronic toxicity studies. *Reprod Toxicol* 27(2):117-132.

Desai VG, Lee T, Moland CL, Branham WS, Von Tungeln LS, Beland FA, Fuscoe JC. 2009. Effect of short-term exposure to zidovudine (AZT) on the expression of mitochondria-related genes in skeletal muscle of neonatal mice. *Mitochondrion* 9(1):9-16.

de Serres FJ, Blanco I, Fernandez-Bustillo E. 2009. Estimates of PI*S and PI*Z Alpha-1 antitrypsin deficiency alleles prevalence in the Caribbean and North, Central and South America. *Monaldi Arch Chest Dis* 71(3):96-105.

DeWitt JC, Shnyra A, Badr MZ, Loveless SE, Hoban D, Frame SR, Cunard R, Anderson SE, Meade BJ, Peden-Adams MM, Luebke RW, Luster MI. 2009. Immunotoxicity of perfluorooctanoic acid and perfluorooctane sulfonate and the role of peroxisome proliferator-activated receptor alpha. *Crit Rev Toxicol* 39(1):76-94.

Ding M, Kisin ER, Zhao J, Bowman L, Lu Y, Jiang B, Leonard S, Vallyathan V, Castranova V, Murray AR, Fadeel B, Shvedova AA. 2009. Size-dependent effects of tungsten carbide-cobalt particles on oxygen radical production and activation of cell signaling pathways in murine epidermal cells. *Toxicol Appl Pharmacol* 241(3):260-268.

Dobrovolskaia MA, Germolec DR, Weaver JL. 2009. Evaluation of nanoparticle immunotoxicity. *Nature Nanotechnol* 4(7):411-414.

Dobrovolsky VN, Bigger CAH, Elespuru RK, Robison TW, Heflich RH. 2009. Detecting PIG-A gene mutation in human red blood cells. *Environ Mol Mutagen* 50(7):562-562.

Dobrovolsky VN, Boctor SY, Twaddle NC, Doerge DR, Bishop ME, Manjanatha MG, Kimoto T, Miura D, Heflich RH, Ferguson SA. 2009. Flow cytometric detection of Pig-A mutant red blood cells using an erythroid-specific antibody: Application of the method for evaluating the *in vivo* genotoxicity of methylphenidate in adolescent rats. *Environ Mol Mutagen* 51(2):138-145.

Dobrovolsky VN, Shaddock JG, Mittelstaedt RA, Manjanatha MG, Miura D, Uchikawa M, Mattison DR, Morris SM. 2009. Evaluation of Macaca mulatta as a model for genotoxicity studies. *Mutat Res* 673(1):21-28.

Duffy RE, Siegel PZ. 2009. Increasing chronic disease epidemiology capacity without increasing workforce: a success story in Ohio. *J Public Health Manag Pract* 15(2):123-126.

Dunnick JK, Nyska A. 2009. Characterization of liver toxicity in F344/N rats and B6C3F1 mice after exposure to a flame retardant containing lower molecular weight polybrominated diphenyl ethers. *Exp Toxicol Pathol* 61:1-12.

Elespuru RK, Agarwal R, Atrakchi AH, Bigger CA, Heflich RH, Jagannath DR, Levy DD, Moore MM, Ouyang Y, Robison TW, Sotomayor RE, Cimino MC, Dearfield KL. 2009. Current and future application of genetic toxicity assays: the role and value of *in vitro* mammalian assays. *Toxicol Sci* 109(2):172-179.

Elespuru RK, Agarwal R, Atrakchi A, Bigger CA, Heflich, RH Jagannath, DR Levy, DD, Moore MM, Ouyang Y, Robison TW, Cimino MC, Dearfield KL. 2009. Future application of genetic toxicity assays. *Environ Mol Mutagen* 50(7):563-563.

Elmore SA, Peddada SD. 2009. Points to consider on the statistical analysis of rodent cancer bioassay data when incorporating historical control data. *Toxicol Pathol* 37(5): 672-676.

Erdely A, Hulderman T, Salmen R, Liston A, Zeidler-Erdely PC, Schwegler-Berry D, Castranova V, Koyama S, Kim YA, Endo M, Simeonova PP. 2009. Cross-talk between lung and systemic circulation during carbon nanotube respiratory exposure. Potential biomarkers. *Nano Lett* 9(1):36-43.

Espandiari P, Rosenzweig B, Zhang J, Zhou Y, Schnackenberg L, Vaidya VS, Goering PL, Brown RP, Bonventre JV, Mahjoob K, Holland RD, Beger RD, Thompson K, Hanig J, Sadrieh N 2009. Age-related differences in susceptibility to cisplatin-induced renal toxicity. *J Appl Toxicol* 30(2):172-82.

Estill CF, Baron PA, Beard JK, Hein MJ, Larsen LD, Rose L, Schaefer FW, 3rd, Noble-Wang J, Hodges L, Lindquist HD, Deye GJ, Arduino MJ. 2009. Recovery efficiency and limit of detection of aerosolized Bacillus anthracis Sterne from environmental surface samples. *Appl Environ Microbiol* 75(13):4297-306.

Fan MQ, Bell AR, Bell DR, Clode S, Fernandes A, Foster PMD, Fry JR, Jiang T, Loizou G, MacNicoll A, Miller BG, Rose M, Shaikh-Omar O, Tran L, White S. 2009. Recombinant expression of aryl hydrocarbon receptor for quantitative ligand-binding analysis. *Anal Biochem* 384(2):279-287.

Fan X, Fang H, Hong H, Perkins R, Shi L, Tong W. 2008. Correlation analysis of external RNA controls reveals its utility for assessment of microarray assay. *Anal Biochem* 385:203-207.

Fan X, Shi L , Fang H , Harris S , Perkins R, Tong W. 2009. Investigation of reproducibility of differentially expressed genes in DNA microarrays through statistical simulation. *BMC Proc.* 3(Suppl 2):S4.

Fang F, Kamel F, Lichtenstein P, Bellocco R, Sparen P, Sandler DP, Ye WM. 2009. Familial aggregation of Amyotrophic Lateral Sclerosis. *Ann Neurol* 66(1):94-99.

Fang H, Harris SC, Su Z, Chen M, Qian F, Shi L, Arasappan D, Ge W, Fan X, Hong H, Xu Z, Turner SA, Bishop ME, Jackson MA, Perkins RG, Tong W. 2009. FDA bioinformatics tool for public use – ArrayTrack.™ *Regul Res Perspect* 8(1).

Fang J, Beland FA. 2009. Long-term exposure to zidovudine delays cell cycle progression, induces apoptosis, and decreases telomerase activity in human hepatocytes. *Toxicol Sci* 111(1):120-30.

Fang F, Quinlan P, Ye W, Barber MK, Umbach DM, Sandler DP, Kamel F. 2009. Workplace exposures and the risk of Amyotrophic Lateral Sclerosis. *Environ Health Perspect* 117(9):1387-92.

Fang JL, McGarrity LJ, Beland FA. 2009. Interference of cell cycle progression by zidovudine and lamivudine in NIH 3T3 cells. *Mutagen* 24(2):33-41.

Feng J, Heinze TM, Xu H, Cerniglia CE, Chen H. 2009. Evidence for significantly enhancing reduction of azo dyes in Escherichia coli by expressed cytoplasmic azoreductase (AzoA) of Enterococcus faecalis. *Prot Peptide Lett* 17(5):578-84.

Ferguson SA, Boctor SY. 2009. Adolescent methylphenidate treatment does not alter adult levels of hedonia in male and female Sprague Dawley rats. *Neurotoxicol Teratol* 31(4):NBTS27.

Ferguson SA, Boctor SY. 2009. Use of food wafers for multiple daily oral treatments in young rats. *J Am Assoc Lab Anim Sci* 48(3):292-5.

Ferguson SA, Delclos KB, Newbold RR, Flynn KM. 2009. Few effects of multi-generational dietary exposure to genistein or nonyl*phenol on sodium solution intake in male and female Sprague Dawley rats. Neurotoxicol Teratol* 31(3):143-8.

Ferguson SA, Garey JD, Smith ME, Paule MG. 2008. Pre and postnatal acrylamide treatment has few effects on preweaning behaviors and developmental landmarks in rats. *Neurotoxicol Teratol epub.*

Ferguson SA, Gopee NV, Paule MG, Howard PC. 2009. Female mini-pig performance of temporal response differentiation, incremental repeated acquisition, and progressive ratio operant tasks. *Behav Proc* 80(1):28-34.

Foley SL, Lynne AM, Nayak RR. 2009. Molecular typing methodologies for microbial source tracking and epidemiological investigations of Gram-negative bacterial foodborne pathogens. *Infection Genet Evol* 9:430-440.

Foley SL, Lynne AM, Nayak RR. 2009. Molecular typing methods of enterobacteriaceae: Escherichia coli, Yersinia, *Salmonella* and Shigella. Book chapter in *Molecular Typing in Bacterial Infections*.

Forester CD, Wells JR. 2009. Yields of carbonyl products from gas-phase reactions of fragrance compounds with OH radical and ozone. *Environ Sci Technol* 43(10):3561-3568.

Frasch HF, Barbero AM. 2009. A paired comparison between human skin and hairless guinea pig skin *in vitro* permeability and tag time measurements for 6 industrial chemicals. *Cutan Ocul Toxicol* 28(3):107-113.

Fu PP, Chiang HM, Xia QS, Chen T, Chen BH, Yin JJ, Wen KC, Lin G and Yu HT. 2009. Quality assurance and safety of herbal dietary supplements. *J Environ Sci Health C-Environ Carcinog Ecotoxicol Rev* 27(2):91-119.

Fu PP, Qingsu X, Lei G, Hongtao Y, Chan PC. 2008. Toxicity of Kava Kava. *J Environ Sci Health Part C – Environ Carcinogen Ecotocicol Rev* 26:89-112.

Gambus A, van Deursen F, Polychronopoulos D, Foltman M, Jones RC, Edmondson RD, Calzada A, Labib K. 2009. A key role for Ctf4 in coupling the MCM2-7 helicase to DNA polymerase alpha within the eukaryotic replisome. *EMBO* 28(19):2992-3004.

Gao Y, Holland RD, Yu L. 2009. Quantitative proteomics for drug toxicity. *Briefings in Functional Genomics and Proteomics*. 8(2):158-166.

Garantziotis S, Li ZW, Potts EN, Kimata K, Zhuo LS, Morgan DL, Savani RC, Noble PW, Foster WM, Schwartz DA, Hollingsworth JW. 2009. Hyaluronan mediates ozone-induced airway hyperresponsiveness in mice. *J Biol Chem* 284(17):1309-11317.

Garey J, Paule MG. 2009. Effects of chronic oral acrylamide exposure on incremental repeated acquisition (learning) task performance in Fischer 344 rats. *Neurotoxicol Teratol* 32(2):220-5.

George N, Chen JJ. 2009. Batch effect estimation of microarray platforms with analysis of variance. In Batch Effect and Noise in Microarry Experiments: Sources and Solutions. *Sources and Solutions*. 75-84.

Ghanayem BI, Bai R, Kissling GE, Travlos G, Hoffler U. 2009. Diet-induced obesity in male mice is associated with reduced fertility and potentiation of acrylamide-induced reproductive toxicity. *Biol Reprod* 82(1):96-104. epub.

Ghanem MM, Battelli LA, Law BF, Castranova V, Kashon ML, Nath J, Hubbs AF. 2009. Coal dust alters beta-naphthoflavone-induced aryl hydrocarbon receptor nuclear translocation in alveolar type II cells. *Part Fibre Toxicol* 6:21.

Gilbert KM, Przybyla-Zawislak BD, Pumford NR, Han T, Fuscoe J, Schnackenberg L, Holland RD, Macmillan-Crow L, Doss JC, Blossom SJ. 2009. Delineating liver events in trichloroethylene-induced autoimmune hepatitis. *Chem Res Toxicol* 22:626-632.

Gohlke JM, Stockton P, Sieber S, Foley J, Portier CJ. 2009. AhR-mediated gene expression in the developing mouse telencephalon. *Neurotoxicol Teratol* 31(4):NBTS17.

Gohlke JM, Stockton P, Sieber S, Foley J, Portier CJ. 2009. AhR-mediated gene expression in the developing mouse telencephalon. *Birth Defects Res Part A – Clin Mol Teratol* 85(5):405-405.

Gopee NV, Roberts DW, Webb P, Cozart CR, Siitonen PH, Latendresse JR, Warbitton AR, Yu WW, Colvin VL, Walker NJ, Howard PC. 2009. Quantitative determination of skin penetration of PEG-coated CdSe quantum dots in dermabraded but not intact SKH-1 hairless mouse skin. *Toxicol Sci* 111(1):37-48.

Greenburg DL, Rusiecki J, Koutros S, Dosemeci M, Patel R, Hines CJ, Hoppin JA, Alavanja MCR. 2008. Cancer incidence among pesticide applicators exposed to captan in the Agricultural Health Study. *Cancer Causes Control* 19(10):1401-1407.

Guo L, Li QZ, Xia QS, Dial S, Chan PC, Fu P. 2009. Analysis of gene expression changes of drug metabolizing enzymes in the livers of F344 rats following oral treatment with kava extract. *Food Chem Toxicol* 47(2):433-442.

Guo L, Mei N, Liao W, Chan PC, Fu PP. Ginkgo biloba extract-induced gene expression changes in xenobiotics metabolism and Myc-centered network. *OMICS*: 14(1):75-90.

Guo L, Shelton, S Moore, M, Manjanatha M. 2009. Acrylamide and glycidamide induce cell gene mutations in lung tissue of Big Blue® mice. *Environ Mol Mutagen* 50(7):570-570.

Guo L, Shi Q, Fang J, Mei N, Ali AA, Lewis SM, Leakey JE, Frankos VH. 2008. Review of usnic acid and Usnea barbata toxicity. *J Environ Sci Health, Part C*. 26:317-338.

Gwinn MR, Leonard SS, Sargent LM, Lowry DT, McKinstry K, Meighan T, Reynolds SH, Kashon M, Castranova V, Vallyathan V. 2009. The role of p53 in silica-induced cellular and molecular responses associated with carcinogenesis. *J Toxicol Environ Health* A 72(23):1509-1519.

Ham JE, Wells JR. 2008. Surface chemistry reactions of a-terpineol [(R)-2-(4-methyl-3-cyclohexenyl)isopropanol] with ozone and air on a glass and a vinyl tile. *Indoor Air* 18(5):394-407.

Ham JE, Wells JR. 2009. Surface chemistry of dihydromyrcenol (2,6-dimethyl-7-octen-2-ol) with ozone on silanized glass, glass, and vinyl flooring tiles. *Atmosph Environ* 43(26):4023-4032.

Hanley KW, Petersen MR, Cheever KL, Luo L. 2009. *N*-acetyl-S-(*n*-propyl)-l-cysteine in urine from workers exposed to 1-bromopropane in foam cushion spray adhesives. *Ann Occup Hyg* 53(7):759-69.

Harper M, Lee EG, Doorn SS, Hammond O. 2008. Differentiating non-asbestiform amphibole and amphibole asbestos by size characteristics. *J Occup Environ Hyg* 5(12):761-770.

Harel L, Costa B, Tcherpakov M, Zapatka M, Oberthuer A, Hansford LM, Vojvodic M, Levy Z, Chen Z, Lee FS, Avigad S, Yaniv I, Shi L, Eils R, Fischer M, Brors B, Kaplan DR, Fainzilber M. 2009. CCM2 mediates death signaling by the TrkA receptor tyrosine kinase. *Neuron* 63:585-591.

Harper M, Slaven JE, Pang TWS. 2009. Continued participation in an asbestos fiber-counting proficiency test with relocatable grid slides. *J Environ Mon* 11(2):434-438.

Harrison JC, Wells, JR. 2009. Gas-phase chemistry of benzyl alcohol: Reaction rate constants and products with OH radical and ozone. *Atmospheric Environ* 43(4):798-804.

He Z. 2009. Fluorogold induces persistent neurological deficits and circling behavior in mice over-expressing human mutant tau. *Curr Neurovascular Res* 6(1):54-61.

Hermon TL, Moore AB, Yu L, Kissling GE, Castora FJ, Dixon D. 2008. Estrogen receptor alpha (ERalpha) phospho-serine-118 is highly expressed in human uterine leiomyomas compared to matched myometrium. *Virchows Arch* 453(6):557-69.

Hettick JM, Ruwona TB, Siegel PD. 2009. Structural elucidation of isocyanate-peptide adducts using tandem mass spectrometry. *J Am Soc Mass Spectrom* 20(8):1567-75.

Hines CJ, Hopf NBN, Deddens JA, Calafat AM, Silva MJ, Grote AA, Sammons DL. 2009. Urinary phthalate metabolite concentrations among workers in selected industries: a pilot biomonitoring study. *Ann Occup Hyg* 53(1):1-17.

Hobbs CA, Recio L, Shepard K, Baldetti C, Winters J, Green A, Allen P, Streicker M, Caspary W, Witt KL. 2009. Enhanced susceptibility to genotoxic damage in Wistar Han rats compared to Fischer 344/N Rats. *Environ Mol Mutagen* 50(7): 584-584.

Hoehle SI, Knudsen GA, Sanders JM, Sipes IG. 2009. Absorption, distribution, metabolism, and excretion of 2,2-Bis(bromomethyl)-1,3-propanediol in male Fischer-344 Rats. *Drug Metab Disp* 37(2): 408-416.

Hoffler U, Hobbie K, Wilson R, Bai R, Rahman A, Malarkey D, Travlos G, Ghanayem BI. 2009. Diet-induced obesity is associated with hyperleptinemia, hyperinsulinemia, hepatic steatosis, and glomerulopathy in C57Bl/6J mice. *Endocrine* 36(2):311-25.

Hogan MB, Piktel D, Hubbs AF, McPherson LE, Landreth KS. 2008. Asthma progression to airway remodeling and bone marrow eosinophil responses in genetically distinct strains of mice. *Ann Allergy Asthma Immunol* 101(6):619-625.

Hong H, Shi, L, Fuscoe J , Goodsaid FM , Mendrick D, Tong W. 2009. Potential sources of spurious associations and batch effects in genome-wide association studies. In Batch Effect and Experimental Shift in Microarray Analysis: Sources and Solutions. 191-202.

Hong H, Hong Q, Tong W. 2009. Accurate prediction and recognition of subfamilies of G protein-coupled receptors from amino acid sequences. *The 2009 International Conference on Bioinformatics and Computational Biology* 3-9.

Hong H, Hong Q, Perkins RG, Shi L, Fang H, Su Z, Dragan YP, Fuscoe J, Tong W. The accurate prediction of protein family from amino acid sequence by measuring features of sequence fragments. *J Comput Biol* 16(12):1671-1688.

Hong H, Perry G, Sorgel F, Gedela S, Akulapalli S. 2009. Editorial: *J Bioequivalence Bioavailability* 1(1):001-002.

Hong H, Teitel CH, James LP, Tong W, Hinson JA, Fuscoe J, Dragan YP. 2008. SELDI-based proteomic determination of hepatic biomarkers of mouse serum following acetaminophen administration. *J Proteom Bioinform* 1(8):424-436.

Hopf NB, Waters MA, Ruder AM. 2009. Cumulative exposure estimates for polychlorinated biphenyls using a job-exposure matrix. *Chemosphere* 76(2):185-93.

Hotchkiss AK, Rider CV, Blystone CR, Wilson VS, Hartig PC, Ankley GT, Foster PM Gray CL, Gray LE. 2008. Fifteen years after "Wingspread" - Environmental endocrine disrupters and human and wildlife health: Where we are today and where we need to go. *Toxicol Sci* 105 (2):235-259.

Howroyd P, Allison N, Foley JF, Hardisty J. 2009. Apparent alveolar bronchiolar tumors arising in the mediastinum of F344 rats. *Toxicol Path* 37(3):351-358.

Hu P, Kinyamu HK, Wang L, Martin J, Archer TK, Teng CT. 2008. Estrogen induces estrogen-related receptor α gene expression and chromatin structural changes in estrogen receptor (ER)-positive and ER-negative breast cancer cells. *J Biol Chem* 283(11):6752-6763.

Il'Yasova D, McCarthy BJ, Erdal S, Shimek J, Goldstein J, Doerge DR, Myers SR, Vineis P, Wishnok JS, Swenberg J, Bigner DD, Davis FG. 2009. Human exposure to selected animal neurocarcinogens: a biomarker-based assessment and implications for brain tumor epidemiology. *J Toxicol Environ Health Part B*. 12:175-187.

Ismailoglu UB, VanScott MR, Fedan JS. 2009. Effects of cytokines on mechanical and epithelial bioelectric responses to methacholine and hyperosmolarity in guinea-pig airways: an *in vitro* study. *Eur J Pharmacol* 612(1-3):115-121.

Jefferson WN, Padilla-Banks E, Goulding EH, Lao SPC, Newbold RR, Williams CJ. 2009. Neonatal exposure to genistein disrupts ability of female mouse reproductive tract to support preimplantation embryo development and implantation. *Biol Reprod* 80(3):425-431.

Jeong S, Cerniglia CE, Greenlees, K. Avilamycin. 70th Joint FAO/Who Expert. 2009.

Jiang T, Bell DR, Clode S, Fan MQ, Fernandes A, Foster PMD, Loizou G, MacNicoll A, Miller BG, Rose M, Tran L, White S. 2009. A truncation in the aryl hydrocarbon receptor of the CRL:WI(Han) rat does not affect the developmental toxicity of TCDD. *Toxicol Sci* 107(2):512-521.

Jing Y, Dowdy JA, Van Scott MR, Fedan JS. 2008. Simultaneous measurement of mechanical responses and transepithelial potential difference and resistance, in guinea-pig isolated, perfused trachea using a novel apparatus: pharmacological characterization. *Eur J Pharmacol* 598(1-3):98-103.

Joseph A, Lee T, Moland CL, Branham WS, Fuscoe JC, Leakey JEA, Allaben WT, Lewis SM, Ali AA, Desai VG. 2009. Effect of (+)-usnic acid on mitochondrial functions as measured by mitochondria-specific oligonucleotide microarray in liver of B6C3F(1) mice. *Mitochondrion* 9(2):149-158.

Joseph P. 2009. Mechanisms of cadmium carcinogenesis. *Toxicol Appl Pharmacol* 238(3):272-9.

Joseph PN, Violanti, JM, Donahue R, Andrew ME, Trevisan M, Burchfiel CM, Dorn J 2009.
Police work and subclinical atherosclerosis. *J Occup Environ Med* 51(6):700-7.

Jung CM, Heinze TM, Schnackenberg L, Mullis L, Elkins SA, Elkins C, Steele RS, Sutherland JB. 2009. Interaction of dietary resveratrol with animal-associated bacteria. *FEMS Microbiol Lett* 297:266-273.

Kagan VE, Bayir HA, Belikova NA, Kapralov O, Tyurina YY, Tyurin VA, Jiang JF, Stoyanovsky DA, Wipf P, Kochanek PM, Greenberger JS, Pitt B, Shvedova AA, Borisenko G. 2009. Cytochrome c/cardiolipin relations in mitochondria: a kiss of death. *Free Radical Biol Med* 46(11):1439-1453.

Kai K, D'Costa S, Sills RC, Kim Y. 2009. Inhibition of the insulin-like growth factor 1 receptor pathway enhances the antitumor effect of cisplatin in human malignant mesothelioma cell lines. *Cancer Lett* 278(1):49-55.

Kalaiselvan P, Vijayakumar S, Hemalatha K, Murkunde YV, Herbert RA, Wells MY. 2009. Mass in the lateral cervical-thoracic region in a male Wistar rat. *Lab Animal* 38(9):288-289.

Kamel F. 2008. Organophosphate insecticides and neurologic dysfunction in the agricultural health study. *Epidemiol* 19(6):S80-S80.

Kang HS, Beak JY, Kim YS, Herbert R and Jetten AM. 2009. Glis3 Is associated with primary cilia and Wwtr1/TAZ and implicated in polycystic kidney disease. *Mol Cell Biol* 29(10):2556-2569.

Kaput J, Ning B. 2009. Nutrigenomics for pet nutrition and medicine. *Compend Cont Educ Pract Vet* 31:40-45.

Kaput J, Chen JJ , Slikker W. 2009. Personalized nutrition and medicine in perinatal development. Book chapter in Developmental Toxicology, 3rd Edition. Edited by D. Hansen, D and B. Abbott. Published by Informa Heathcare USA. 123-144.

Kaput J, Cotton RG, Hardman L, Watson M, Al-Aqeel AI, Al-Aama JY, Al-Mulla F, Alonso S, Aretz S, Auerbach AD, Bapat B, Bernstein IT, Bhak J, Bleoo SL, Blöcker H, Brenner SE, Burn J, Bustamante M, Calzone R, Cambon-Thomsen A, Cargill M, Carrera P, Cavedon L, Cho YS, Chung YJ, Claustres M, Cutting G, Dalgleish R, den Dunnen JT, Díaz C, Dobrowolski S, dos Santos MR, Ekong R, Flanagan SB, Flicek P, Furukawa Y, Genuardi M, Ghang H, Golubenko MV, Greenblatt MS, Hamosh A, Hancock JM, Hardison R, Harrison TM, Hoffmann R, Horaitis R, Howard HJ, Barash CI, Izagirre N, Jung J, Kojima T, Laradi S, Lee YS, Lee JY, Gil-da-Silva-Lopes VL, Macrae FA, Maglott D, Marafie MJ, Marsh SG, Matsubara Y, Messiaen LM, Möslein G, Netea MG, Norton ML, Oefner PJ, Oetting WS, O'Leary JC, de Ramirez AM, Paalman MH, Parboosingh J, Patrinos GP, Perozzi G, Phillips IR, Povey S, Prasad S, Qi M, Quin DJ, Ramesar RS, Richards CS, Savige J, Scheible DG, Scott RJ, Seminara D, Shephard EA, Sijmons RH, Smith TD, Sobrido MJ, Tanaka T, Tanaka SV, Taylor GR, Teague J, Töpel, T, Ullman-Cullere M, Utsunomiya J, van Kranen HJ, Vihinen M, Webb E, Weber TK, Yeager M, Yeom YI, Yim SH, Yoo HS. 2009. Planning the human variome project: the Spain report. *Human Mutation* 30:496-510.

Karlsson A, Ungerback J, Rasmussen A, French JE, Soderkvist P. 2008. Notch1 is a frequent mutational target in chemically induced lymphoma in mouse. *Int J Cancer* 123(11):2720-2724.

Kashimshetty R, Desai VG, Kale VM, Lee T, Moland CL, Branham WS, New LS, Chan EC, Younis H, Boelsterli UA 2009. Underlying mitochondrial dysfunction triggers flutamide-induced oxidative liver injury in a mouse model idiosyncratic drug toxicity. *Toxicol Appl Pharmacol* 238(2):150-159.

Kavlock RJ, Austin CP, Tice RR. 2009. Toxicity testing in the 21st Century: Implications for human health risk assessment. *Risk Anal* 29(4):485-487.

Keane M, Stone S, Chen B, Slaven J, Schwegler-Berry D, Antonini J. 2009. Hexavalent chromium content in stainless steel welding fumes is dependent on the welding process and shield gas type. *J Environ Monit* 11(2):418-24.

Keenan C, Elmore S, Francke-Carroll S, Kemp R, Kerlin R, Peddada S, Pletcher J, Rinke M, Schmidt SP, Taylor I, Wolf DC. 2009. Best practices for use of historical control data of proliferative rodent lesions. *Toxicol Pathol* 37(5):679-693.

Keenan C, Elmore S, Francke-Carroll S, Kerlin R, Peddada S, Pletcher J, Rinke M, Schmidt SP, Taylor I, Wolf DC. 2009. Potential for a global historical control database for proliferative rodent lesions. *Toxicol Pathol* 37(5):677-678.

Khan AA, Ponce ER, Nawaz MS, Cheng C, Khan JA, Summage-West CV. 2009. Identification and characterization of class 1 integron resistance gene cassettes among *Salmonella* strains isolated from imported seafood. *Appl Environ Microbiol* 75(4):1192-1196.

Khan SA, Sung K, Nawaz MS, Cerniglia CE, Tamplin ML, Phillips RW, Kelley LC. 2009. The survivability of Bacillus anthracis (Sterne strain) in processed liquid eggs. *Food Microbiol* 26:123-127.

Kim, S., Kweon, O., and Cerniglia, C.E. 2009. Proteomic applications to elucidate bacterial aromatic hydrocarbon metabolic pathways. *Current Opinion Microbiology* 12:301-309.

King-Herbert, AP, Sills, RC , Bucher, JR. 2009. Commentary: update on animal models for NTP. *Tox Path* 38(1):180-181.

Kisby GE, Olivas A, Park T, Churchwell M, Doerge D, Samson LD, Gerson SL, Turker MS. 2009. DNA repair modulates the vulnerability of the developing brain to alkylating agents. *DNA Repair* 8(3):400-412.

Kissling GE, Malarkey DE, Vallant MK, Johnson JD, Hejtmancik MR, Herbert RA, Boorman GA. 2009. Evaluation of dichloroacetic acid for carcinogenicity in genetically modified Tg.AC hemizygous and p53 haploinsufficient Mice. *Toxicol Sci* 107(1):19-26.

Kodell RL, Pearce BA, Baek S, Moon H, Ahn H, Young JF, Chen JJ. 2009. A model-free ensemble method for class prediction with application to biomedical decision making. *Artificial Intell Med* 46(3):267-276.

Knudsen, GA, Cheng Y, Kuester RK, Hooth MJ, Sipes IG. 2009. Effects of dose and route on the disposition and kinetics of 1-butyl-1-methylpyrrolidinium chloride in male F344 rats. *Drug Metab Disp* 37(11):2171-2177.

Konduru NV, Tyurina YY, Feng W, Basova LV, Belikova NA, Bayir H, Clark K, Rubin M, Stolz D, Vallhov H, Scheynius A, Witasp E, Fadeel B, Kichambare PD, Star A, Kisin ER, Murray AR, Shvedova AA, Kagan VE. 2009. Phosphatidylserine targets single-walled carbon nanotubes to professional phagocytes *in vitro* and *in vivo*. *PLoS ONE* 4(2):e4398.

Koujitani T, Ton TV, Lahousse SA, Hong HH, Wakamatsu N, Sills RC. 2008. K-ras cancer gene mutations in lung tumors from female Swiss (CD-1) mice exposed transplacentally to 3'-azido-3'-deoxythymidine. *Environ Mol Mutagen* 49 (9):720-6.

Krieg EF Jr., Butler MA. 2009. Blood lead, serum homocysteine, and neurobehavioral test performance in the third National Health and Nutrition Examination Survey. *Neuro Toxicol* 30(2):281-289.

Krieg EF Jr., Butler MA, Chang MH, Liu T, Yesupriya A, Lindegren ML, Dowling N 2009. Lead and cognitive function in ALAD genotypes in the third National Health and Nutrition Examination Survey. *Neurotoxicol Teratol* 31(6):364-371.

Kreiss K, Hubbs A. 2009. Letter to the Editor: RE: Galbraith D and Weill D. Popcorn lung and bronchiolitis obliterans: a critical appraisal. *Int Arch Occup Environ Health* 82:407-416.

Kuempel ED, Wheeler MW, Smith RJ, Vallyathan V, Green FH. 2009. Contributions of dust exposure and cigarette smoking to emphysema severity in coal miners in the United States. *Am J Respir Crit Care Med* 180(3):257-264.

Latendresse JR, Bucci TJ, Olson GR, Mellick PW, Weis CC, Thorn BT, Newbold R, Delclos KB. 2009. Genistein and ethinyl estradiol dietary exposure in multigenerational and chronic studies induce similar proliferative lesions in mammary gland of male Sprague Dawley rats. *Reprod Toxicol* 28(3):342-353.

Lawryk NJ, Feng HA, Chen BT. 2009. Laboratory evaluation of a field-portable sealed source X-ray fluorescence spectrometer for determination of metals in air filter samples. *J Occup Environ Hyg* 6(7):433-445.

Lea IA, Jackson MA, Dunnick JK. 2009. Pathways to colorectal cancer. *Mutat Res* 670:96-98.

LeBlanc AJ, Cumpston JL, Chen BT, Frazer D, Castranova V, Nurkiewicz TR. 2009. Nanoparticle inhalation impairs endothelium-dependent vasodilation in subepicardial arterioles. *J Toxicol Environ Health* A 72(24):1576-1584.

Lee EG, Harper M, Bowen RB and Slaven J. 2009. Evaluation of COSHH essentials: methylene chloride, isopropanol, and acetone exposures in a small printing plant. *Ann Occup Hyg* 53(5):463-74.

Lee L, Flemmer M, Lee EG, Harper M, Lin MI, Groves W, Freivalds A, Slaven J. 2009. A novel physiologic sampling pump capable of rapid response to breathing. *J Environ Monit* 11(5):1020-7.

Levine KE, Stout MD, Ross GT, Essader AS, Perlmutter JM, Grohse PM, Fernando RA, Lang M, Collins BJ. 2009. Validation of a method for the determination of total chromium in rat feces by inductively coupled plasma optical emission spectrometry. *Anal Lett* 42(17):2729-2746.

Lewis SM, Ali AA, Badgley HL, Allaben WT, Latendresse JR, Patton R, Leakey JE. 2009. The Zucker rat: a model for diabetic renal nephropathy. *J Amer Assoc Lab Anim Sci* 48(5):582-582.

Li S, Nagothu K, Desai VG, Lee T, Branham WS, Moland CL, Megyesi J, Crew M, Portilla D. Proximal tubule PPARa confers protection during acute kidney injury. *J Amer Soc Nephrology.* epub. 2009.

Li Y, Limmon GV, Imani F, Teng C. 2009. Induction of lactoferrin gene expression by innate immune stimuli in mouse mammary epithelial HC-11 cells. *Biochimie* 91(1):58-67.

Li Z, Shi L, Pearce M, Wang Y, Guo L, Branham WS, Chen T. 2009. Time-course study of microRNA gene expression in liver of mice treated with one dose of *N*-ethyl-*N*-nitrosourea. *Environ Mol Mutagen* 50(7):558-558.

Li Z, Su Z, Wen Z, Shi L, Chen T. 2009. Microarray platform consistency is revealed by biologically functional analysis of gene expression profiles. *BMC Bioinformatics* 10(11):S12.

Lowe BD, Krieg EF. 2009. Relationships between observational estimates and physical measurements of upper limb activity. *Ergonomics* 52(5):569-83.

Lowe BD, Schrader SM, Breitenstein MJ. 2009. Letter to the Editor. *Appl Ergon* 41(1):173-4.

Lu Y, Chang Q, Zhang Y, Beezhold K, Rojanasakul Y, Zhao H, Castranova V, Shi X, Chen F. 2009. Lung cancer-associated JmjC domain protein mdig suppresses formation of tri-methyl lysine 9 of histone H3. *Cell Cycle* 8(13):2101-9.

Ma J, Jiang CG, Lin YZ, Wang XF, Zhao LP, Xiang WH, Shao YM, Shen RX, Kong XG, Zhou JH. 2009. *In vivo* evolution of the gp90 gene and consistently low plasma viral load during transient immune suppression demonstrate the safety of an attenuated equine infectious anemia virus (EIAV) vaccine. *Arch Virol* 154(5):867-873.

Ma Y, Ding ZY, Qian Y, Wan YW, Tosun K, Shi XL, Castranova V, Harner EJ, Guo NL. 2009. An integrative genomic and proteomic approach to chemosensitivity prediction. *Internat J Oncol* 34(1):107-115.

Macher J, Chen B, Rao C. 2008. Chamber evaluation of a personal, bioaerosol cyclone sampler. *J Occup Environ Hyg* 5(11):702-712.

Macher J, Chen B, Rao C. 2008. Field evaluation of a personal, bioaerosol cyclone sampler. *J Occup Environ Hyg* 5(11):724-734.

Manjanatha MG, Shelton SD, Dobrovolsky VN, Shaddock JG, McGarrity LG, Twaddle NW, Moore MM, Mattison DR, Slikker W, Jr., Morris SM. 2009. Evaluation of mutagenic mode of action in Big Blue mice fed methylphenidate for 24 weeks. *Mutat Res* 680(1-2):43-8.

Marchetti F, Bishop J, Xiu LW, Wyrobek AJ. 2009. Chromosomal mosaicism in mouse two-cell embryos after paternal exposure to acrylamide. *Toxicol Sci* 107(1):194-205.

Marczak ED, Jinsmaa Y, Myers PH, Blankenship T, Wilson R, Balboni G, Salvadori S, Lazarus LH. 2009. Orally administered H-Dmt-Tic-Lys-NH-CH2-Ph (MZ-2), a potent mu/delta-opioid receptor antagonist, regulates obese-related factors in mice. *Eur J Pharmacol* 616(1-3):115-21.

Marques MM, Sidarus MC, Beland FA, Antunes AMM. 2009. Chemical and enzymatic oxidation of 2-hydroxynevirapine, a metabolite of the HIV-1 reverse transcriptase inhibitor nevirapine. *Toxicol Lett* 189:S102.

Martin CJ, Antonini JM, Doney BC. 2009. A case report of elevated blood cadmium. *Occup Med*-(Lond) 59(2):130-132.

Mattie MD, McElwee MK, Freedman JH. 2008. Mechanism of copper-activated transcription: Activation of AP-1, and the JNK/SAPK and p38 signal transduction pathways. *J Mol Biol* 383(5):1008-1018.

McBurney RN, Hines WM, Von Tungeln LS, Schnackenberg L, Beger R, Moland, CL, Han T, Fuscoe J, Chang C, Chen JJ, Su Z, Fan X, Tong W, Booth SA, Balasubramanian R, Courchesne, PL, Campbell JM, Graber A, Guo Y, Juhasz PJ, Li TY, Lynch MD, Morel NM, Plasterer TN, Takach EJ, Zeng C, Beland FA. 2009. The liver toxicity biomarker study: phase I design and preliminary results. *Toxicol Path* 37(1):52-64.

McCabe-Sellers BJ, Lovera D, Nuss H, Wise CK, Ning B, Teitel CH, Clark BS, Toennessen T, Green BL, Bogle ML, Kaput J. 2008. Personalizing nutrigenomics research through community-based participatory research and omics technologies. *OMICS* 12(4):263-272.

McDaniel LP, Guo XQ, Doerge DR, Heflich RH, Mei N. 2009. Mutagenicity of acrylamide and glycidamide in rat thyroid. *Environ Mol Mutagen* 50(7):570-570.

McElwee MK, Song MO, Freedman JH. 2009. Copper activation of NF-kappaB signaling in HepG2 cells. *J Mol Biol* 393(5):1013-21.

McKean-Cowdin R, Barnholtz-Sloan J, Inskip PD, Ruder AM, Butler M, Rajaraman P Razavi P, Patoka J, Wiencke JK, Bondy ML, Wrensch M. 2009. Associations between polymorphisms in DNA repair genes and glioblastoma. *Cancer Epidemiol Biomarkers Prev* 18(4):1118-1126.

McKernan JL, Toraason MA, Fernback JE, Petersen MR. 2009. Presence of tungsten-containing fibers in tungsten refining and manufacturing processes. *Ann Occup Hyg* 53(3):215-24.

Mei N, Chen T, Godar DE, Moore M. 2009. UVA-induced photomutagenicity of retinyl palmitate. *Mutation Res* 677:105-106.

Mei N, Fuscoe J, Lobenhofer EK, Guo L. 2009. Application of microarray-based analysis of gene expression in the field of toxicogenomics. In Rat Genomics: gene identification, functional genomics and model applications.

Mei N, Hu J, Xia Q, Fu PP, Moore M, Chen T. 2009. Cytotoxicity and mutagenicity of retinol with ultraviolet A irradiation in mouse lymphoma cells. T*oxicol* In Vitro. e-pub.

Mei N, McDaniel LP, Guo L, Dial SL, Manjanatha MG. 2009. Liver gene expression changes in mice exposed to acrylamide. *Environ Mol Mutagen* 50(7):558-558.

Melchior WB, Tolleson WH. 2009. A functional quantitative PCR assay for ricin, Shiga toxin, and related ribosome-inactivating proteins. *Anal Biochem* 396(2):204-211.

Meng F, Knapp GW, Green T, Ross J, Parsons BL. 2010. K-ras mutant fraction in A/J mouse lung increases as a function of benzo[a]pyrene dose. *Environ Mol Mutag* 51(2):146-55

Millett C, Yamashita M, Heller M, Yu L, Veenstra TD, Zhang YE. 2009. A negative feedback control of transforming growth factor-beta signaling by glycogen synthase kinase 3-mediated Smad3 linker phosphorylation at Ser-204. *J Biol Chem* 284(30):19808-19816.

Mittelstaedt RA, Shaddock JG, Heflich RH. 2009. Flow cytometry analysis of responses in the *in vitro* micronucleus assay. *Environ Mol Mutagen* 50(7):581-581.

Miura D, Dobrovolsky VN, Kimoto T, Kasahara Y, Heflich RH. 2009. Accumulation and persistence of Pig-A mutant peripheral red blood cells following treatment of rats with single and split doses of *N*-ethyl-*N*-nitrosourea. *Mutation Res* 677(1-2):86-92.

Morgan DL, Flake GP, Kirby J, Palmer SM. 2008. Comments on respiratory toxicity of diacetyl in C57Bl/6 mice – Response. *Toxicol Sci* 105 (2):433-434.

Morris SM, Dobrovolsky VN, Shaddock JG, Mittelstaedt RA, Bishop ME, Manjanatha MG, Shelton SD, Doerge DR, Twaddle NC, Chen JJ, Lin CJ, Paule MG, Slikker W Jr., Hotchkiss CE, Petibone D, Tucker JD, Mattison DR. 2009. The genetic toxicology of methylphenidate hydrochloride in non-human primates. *Mutat Res* 673(1):59-66.

Morris JB, Hubbs AF. 2009. Inhalation dosimetry of diacetyl and butyric acid, two components of butter flavoring vapors. *Toxicol Sci* 108(1):173-183.

Morrison JP, Ton TV, Collins JB, Switzer RC, Little PB, Morgan DL, Sills RC. 2009. Gene expression studies reveal that DNA damage, vascular perturbation, and inflammation contribute to the pathogenesis of carbonyl sulfide neurotoxicity. *Toxicol Pathol* 37(4):502-511.

Moser GJ, Foley J, Burnett M, Goldsworthy TL, Maronpot R. 2009. Furan-induced dose-response relationships for liver cytotoxicity, cell proliferation, and tumorigenicity (furan-induced liver tumorigenicity). *Exp Toxicol Pathol* 61(2):101-111.

Msiska Z, Pacurari M, Mishra A, Leonard SS, Castranova V, Vallyathan V. 2009. DNA double strand breaks by asbestos, silica and titanium dioxide: possible biomarker of carcinogenic potential? *Am J Respir Cell Mol Biol.* epub.

Murphy E, Andrew L, Lee KL, Dilts DA, Nunez L, Fink PS, Ambrose K, Borrow R, Findlow J, Taha MK, Deghmane AE, Kriz P, Musilek M, Kalmusova J, Caugant DA, Alvestad T, Mayer LW, Sacchi CT, Wang X, Martin D, Von Gottberg A, Plessis MD, Klugman KP, Anderson AS, Jansen KU, Zlotnick GW, Hoiseth SK. 2009. Sequence diversity of the factor H binding protein vaccine candidate in epidemiological relevant strains of serogroup B neisseria meningitidis. *J Infect Dis* 200(3):379-389.

Murphy WJ, Byrne DC, Gauger D, Ahroon WA, Berger E, Gerges SNY, McKinley R, Witt B, Krieg EF. 2009. Results of the National Institute for Occupational Safety and Health-US Environmental Protection Agency interlaboratory comparison of American National Standards Institute S12.6-1997 Methods A and B. *J Acoust Soc Amer* 125(5):3262-3277.

Murray AR, Kisin E, Leonard SS, Young SH, Kommineni C, Kagan VE, Castranova V, Shvedova AA. 2009. Oxidative stress and inflammatory response in dermal toxicity of single-walled carbon nanotubes. *Toxicol* 257(3):161-71.

Myers MB, Mittelstaedt RA, Heflich RH. 2009. Using X174 DNA as an exogenous reference for measuring mitochondrial DNA copy number. *BioTechniques* 47(4):867-869.

Nawaz MS, Khan AA, Khan SA, Sung K, Kerdahi KF, Steele RS. 2009. Molecular characterization of tetracycline-resistant genes and integrons from avirulent strains of Escherichia coli isolates from catfish. *Appl Environ Microbiol* 6(5):553-559.

Nel, AE, Madler, L, Velegol, D, Xia, T, Hoek, EMV, Somasundaran, P, Klaessig, F, Castranova, V, Thompson, M. 2009. Understanding biophysicochemical interactions at the nano-bio interface. *Nature Materials* 8(7):543-557.

Newbold RR, Jefferson WN, Padilla-Banks E. 2009. Prenatal exposure to bisphenol at environmentally relevant doses adversely affects the murine female reproductive tract later in life. *Environ Health Perspect* 117(6):879-85.

Newbold RR, Padilla-Banks E, Jefferson WN. 2009. Environmental estrogens and obesity. *Mol Cell Endocrinol* 304(1-2): 84-9.

Nurkiewicz TR, Porter DW, Hubbs AF, Stone S, Chen BT, Frazer DG, Boegehold MA, Castranova V. 2009. Pulmonary Nanoparticle exposure disrupts systemic microvascular nitric oxide signaling. *Toxicol Sci* 110(1):191-203.

Nyska A, Cunningham M, Snell M, Malarkey D, Sutton D, Dunnick JK. 2009. The pivotal role of electron microscopic evaluation of the cardiotoxicity of bis(2-chloroethoxy)methane in rats and mice. *Toxicol Pathol* 37(7):873-77.

O'Callaghan JP, Sriram K, Miller DB. 2008. Defining "neuroinflammation" lessons from MPTP- and methamphetamine-induced neurotoxicity. *Ann NY Acad Sci* 1139(1):318-330.

Olivier M, Petitjean A, Teague J, Forbes S, Dunnick JK, den Dunnen JT, Langerod A, Wilkinson JM, Vihinen M, Cotton RGH, Hainaut P. 2009. Somatic mutation databases as tools for molecular epidemiology and molecular pathology of cancer: proposed guidelines for Improving data collection, distribution, and Integration. *Human Mutat* 30(3): 275-282.

O'Reilly EJ, Chen HL, Gardener H, Gao X, Schwarzschild MA, Ascherio A. 2009. Smoking and Parkinson's Disease: Using parental smoking as a proxy to explore causality. *Amer J Epidemiol* 169(6):678-682.

Parsons BL, Meng F. 2009. K-ras mutation in the screening, prognosis, and treatment of cancer. *Biomark Med* 3(6):757-769.

Patterson T, Li M, Morris S, Rodriguez J, Slikker W, Mattison D, Paule M. 2009. The effects of chronic methylphenidate treatment on the performance of rhesus monkeys in the NCTR operant test battery. *Neurotoxicol Teratol* 31(4): NBTS45.

Paule M. 2009. Alteration in nonhuman primate brain function as a consequence of developmental exposure to drugs of abuse. *Neurotoxicol Teratol* 31(4):NBTS57.

Paule MG. 2008. Automated assessment of cognitive function in Macaques. In Critical Contributions of Primate Models for Biopharmaceutical Drug Development.

Paule MG. 2009. The nonhuman primate as a translational model for pesticide in research. In *Hayes' Handbook of Pesticide Toxicology*.

Pham AN, Wang J, Fang JL, Gao X, Zhang YL, Blower PE, Sadee WG, Huang Y. 2009. Pharmacogenomics approach reveals MRP1 (ABCC1)-mediated resistance to geldanamycins. *Pharm Res* 26(4):936-945.

Pogribny IP. 2009. Genomic instability induced by heat-inactivated bacteria: implication to tumorigenesis. *Cell Cycle* 8(13):1983.

Pogribny IP, Beland FA. 2009. DNA hypomethylation in the origin and pathogenesis of human diseases. *Cellular and Molecular Life Sci* 66(14):2249-2261.

Pogribny IP, Muskhelishvili L, Tryndyak VP and Beland FA. 2009. The tumor-promoting activity of 2-acetylaminofluorene is associated with disruption of the p53 signaling pathway and the balance between apoptosis and cell proliferation. *Toxicol Appl Pharmacol* 235(3):305-11.

Pogribny IP, Shpyleva SI, Muskhelishvili L, Bagnyukova TV, James SJ, Beland FA. 2009. Role of DNA damage and alterations in cytosine DNA methylation in rat liver carcinogenesis induced by a methyl-deficient diet. *Mutat Res* 669(1-2):56-62.

Pogribny IP, Tryndyak VP, Bagnyukova TV, Melny S, Montgomery B, Ross SA, Latendresse JR, Rusyn I, Beland FA. 2009. Hepatic epigenetic phenotype predetermines individual susceptibility to hepatic steatosis in mice fed a lipogenic methyl-deficient diet. *J Hepatol* 51(1):176-86.

Rafii F, Park M, Carman RJ. 2009. Characterization of an ATP binding cassette from Clostridium perfringens with homology to an ABC transporter from Clostridium hathewayi. *Anaerobe* 15:116-121.

Rafii F, Sutherland JB, Cerniglia CE 2008. Effects of treatment with antimicrobial agents on the human colonic microflora. *Therapeut Clin Risk Management* 4(6):1343-1358.

Rafii F, Williams AJ, Park M, Sims LM, Heinze TM, Cerniglia CE, Sutherland JB. 2009. Isolation of bacterial strains from bovine fecal microflora capable of degradation of ceftiofur. *Vet Microbiol* 139(1-2):89-96.

Rahman MF, Schrand A, Hussain S, Schlager J, Smith D, Ali SF. 2009. Metallic nanoparticles and their toxicity assessment. Nanomedicine and Nanobiology 2(5):544-68

Rahman MF, Wang J, Patterson TA, Saini UT, Robinson BL, Newport GD, Murdock RC, Schlager JJ, Hussain SM, Ali SF. 2009. Expression of genes related to oxidative stress in the mouse brain after exposure to silver-25 nanoparticles. *Toxicol Lett* 187:15-21.

Rajaraman P, Brenner AV, Butler MA, Wang SS, Pfeiffer RM, Ruder AM, Linet MS, Yeager M, Wang ZM, Orr N, Fine HA, Kwon D, Thomas G, Rothman N, Inskip PD, Chanock SJ. 2009. Common variation in genes related to innate immunity and risk of adult glioma. *Cancer Epidemiol Biomarkers Prev* 18(5):1651-1658.

Ramot Y, Nyska A, Lieuallen W, Maly A, Zlotogorski A, Flake G, Kissling GE, Brix A, Malarkey DE, Hooth MJ. 2009. Inflammatory and chloracne-like skin lesions in B6C3F1 mice exposed to 3,3',4,4'-tetrachloroazobenzene for 2 years. *Toxicol* 265(1-2):1-9.

Ray PC, Yu HT, Fu PP. 2009. Toxicity and environmental risks of nanomaterials: challenges and future needs. *J Environ Sci Health C-Environ Carcinogen Ecotoxicol Rev* 27(1):1-35.

Recio L, Hobbs-Riter C, Shepard K, Baldetti C, Streicker M, Winters J, Caspary W, Witt KL. 2008. Combined protocol for simultaneous measurement of micronucleated erythrocyte frequencies and DNA damage in rodents. *Environ Mol Mutangen* 49(7):574-574.

Reynolds TL, Barnes HJ, Wolfe B, Lu L, Camp DM, Malarkey DE. 2009. Bilateral nocardial endophthalmitis in a prothonotary warbler (Protonotaria citrea). *Vet Pathol* 46(1):120-123.

Ritter L, Nichol K, Kirby G, Cerniglia CE, Bulder A, Anadon A. Monensin. 2009. 70th Joint FAO/WHO Expert Committee on Food Additives.

Roberts G, Cerniglia CE, Neto JP. Tylosin. 2009. 70th Joint FAO/WHO Expert Committee on Food Additives.

Rodriguez JS, Morris SM, Hotchkiss CE, Doerge DR, Allen RR, Mattison DR, Paule MG. 2009. The effects of chronic methylphenidate administration on operant test battery performance in juvenile rhesus monkeys. *Neurotoxicol Teratol* 32(2):142-51.

Rosas-Hernandeez H, Jiménez-Badillo S, Martinez-Cuevas P, Gracia-Espino E, Terrones H, Terrones M, Hussain S, Ali SF, Gonzalez C. 2009. Effects of 45-nm silver nanoparticles on coronary endothelial cells and isolated rat aortic rings. *Toxicol Lett* 191:305-313.

Ross PK, Woods CG, Bradford BU, Kosyk S, Gatti DM, Cunningham ML, Rusyn I. 2009. Time-course comparison of xenobiotic activators of CAR and PPAR alphin mouse liver. *Toxicol Appl Pharmacol* 235(2):199-207.

Ruder AM, Butler MA, Sanderson WT, Carreon T, Waters MA, Zivkovich ZE. 2009. The NIOSH retrospective pesticide reference database. *J Agric Saf Health* 15(2):143-56.

Ruder AM, Carreon T, Butler MA, Calvert GM, Davis-King KE, Waters MA, Schulte PA, Mandel JS, Morton RF, Reding DJ, Rosenman KD. 2009. Exposure to farm crops, livestock, and farm tasks and risk of glioma: the Upper Midwest Health Study. *Am J Epidemiol* 169(12):1479-91.

Ryman-Rasmussen JP, Tewksbury EW, Moss OR, Cesta MF, Wong BA, Bonner JC. 2009. Inhaled multiwalled carbon nanotubes potentiate airway fibrosis in murine allergic asthma. *Amer J Respir Cell Mol Biol* 40(3):349-358.

Sager TM, Castranova V. 2009. Surface area of particle administered versus mass in determining the pulmonary toxicity of ultrafine and fine carbon black: comparison to ultrafine titanium dioxide. *Part Fibre Toxicol* 6:15. epub.

Sanders JM, Bucher JR, Peckham JC, Kissling GE, Hejtmancik MR, Chhabra RS. 2009. Carcinogenesis studies of cresols in rats and mice. *Toxicol* 257(1-2):33-39.

Savolainen SM, Foley JF, Elmore SA. 2009. Histology atlas of the developing mouse heart with emphasis on E11.5 to E18.5. *Toxicol Pathol* 37(4): 395-414.

Schindler EM, Hindes A, Gribben EL, Burns CJ, Yin Y, Lin MH, Owen RJ, Longmore GD, Kissling GE, Arthur JSC, Efimova T. 2009. p38 delta mitogen-activated protein kinase is essential for skin tumor development in mice. *Cancer Res* 69(11):4648-4655.

Schenker MB, Pinkerton KE, Mitchell D, Vallyathan V, Elvine Kreis B, Green FHY. 2009. Pneumoconiosis from agricultural dust exposure among young California farmworkers. *Environ Health Perspect* 117(6):988-994.

Schmued LC, Bowyer JF, Cozart MA, Heard DW, Binienda ZK, Paule M. 2008. Introducing Black-Gold II, a highly soluble gold phosphate complex with several unique advantages for the histochemical localization of myelin. *Brain Res* 1229:210-217.

Schnackenberg L, Mendrick D. 2009. Genomic and metabolomic advances in the indentification of disease and adverse event biomarkers. *Biomark Med* 3(5):605-615.

Schnackenberg L, Chen M, Sun J, Holland RD, Dragan YP, Tong W, Welsh WJ, Beger R. 2009. Evaluations of the trans-sulfuration pathway in multiple liver toxicity studies. *Toxicol Appl Pharmacol* 235:25-32.

Schulte PA, Schubauer-Berigan MK, Mayweather C, Geraci CL, Zumwalde R, McKernan JL. 2009. Issues in the development of epidemiologic studies of workers exposed to engineered nanoparticles. *J Occup Environ Med* 51(3):323-335.

Sharma H, Ali SF, Hussain S, Schlager J, Sharma A. 2009. Influence of engineered nanoparticles from metals on the blood-brain barrier permeability, cerebral blood flow, brain edema and neurotoxicity. An experimental study in the rat and mice using biochemical and morphological approaches. *J Nanosci Nanotech* 9(8):5055-5072.

Sharma H, Ali SF , Tian ZR, Hussain S, Schlager J, Sjöquist PO, Sharma A, Muresanu DF. 2009. Chronic treatment with nanoparticles exacerbate hyperthermia induced blood-barrier breakdown, cognitive dysfunction and brain pathology in the rat. Neuroprotective effects of nanowired-antioxidant compound H-290/51. *J Nanosci Nanotech* 9(8):5073-5090.

Shvedova AA, Kisin ER, Porter D, Schulte P, Kagan VE, Fadeel B, Castranova V. 2009. Mechanisms of pulmonary toxicity and medical applications of carbon nanotubes: Two faces of Janus? *Pharmacol Ther* 121(2):192-204.

Siegel PD, Fedorowicz A, Butterworth L, Law B, Anderson SE, Snyder J, Beezhold D. 2009. Physical-chemical and solvent considerations in evaluating the influence of carbon chain length on the skin sensitization activity of 1-bromoalkanes. *Toxicol Sci* 107(1):78-84.

Silver SR, Whelan EA, Deddens JA, Steenland NK, Hopf NB, Waters MA, Ruder AM, Prince MM, Yong LC, Hein MJ, Ward EM. 2009. Occupational exposure to polychlorinated biphenyls and risk of breast cancer. *Environ Health Perspect* 117(2):276-82.

Simon KC, Chen HL, Gao X, Schwarzschild MA, Ascherio A. 2009. Reproductive factors, exogenous estrogen use, and risk of Parkinson's Disease. *Movement Disorders* 24(9):1359-1365.

Smeltzer MS, Lee CY, Harik N, Hart ME. 2009. The molecular basis of pathogenicity. In The Staphylococci in Human Disease.

Smith JP, Martin A, Sammons DL, Striley C, Biagini R, Quinn J, Cope R, Snawder JE. 2009. Measurement of methamphetamine on surfaces using surface plasmon resonance. *Toxicol Mech Meth* 19(6-7):416-21.

Smith ME, Gopee NV, Ferguson SA. 2009. Preferences of minipigs for environmental enrichment objects. *J Am Assoc Lab Anim Sci* 48(4):391-4.

Smith MV, Boyd WA, Kissling GE, Rice JR, Snyder DW, Portier CJ, Freedman JH. 2009. A discrete time model for the analysis of medium-throughput *C. elegans* growth data. *PLoS ONE* 4(9):e7018.

Song MO, Li J, Freedman JH. 2009. Physiological and toxicological transcriptome changes in HepG2 cells exposed to copper. *Physiol Genomics* 38(3):386-401.

Song W, Ruder AM, Hu L, Li Y, Ni R, Shao W, Kaslow RA, Butler MA, Tang J. 2009. Genetic epidemiology of glioblastoma multiforme: Confirmatory and new findings from analyses of human leukocyte antigen alleles and motifs. *PLoS ONE* 4(9): e7157.

Soung N, Park J, Yu L, Lee KH, Lee J, Bang JK, Veenstra TD, Rhee K, Lee KS. 2009. Plk1-dependent and -independent roles of an ODF2 splice variant, hCenexin1, at the centrosome of somatic cells. *Devel Cell* 16(4):539-550.

Starlard-Davenport A, Tryndyak V, Beland F, Pogribny I. 2009. Role of altered hepatic microRNA expression in the pathogenesis of nonalcoholic hepatosteatosis in mice induced by methyl-deficiency. *Environ Mutagen* 50(7):575-575.

Stewart G, Jiao YG, Valente EJ, Fu PP, Li TQ, Hu ZZ, Yu HT. 2009. Photochemical reaction of 9-nitro-substituted anthracene-like molecules 9-methyl-10-nitroanthracene and 12-methyl-7-nitrobenz[a] anthracene. *J Photochem Photobiol a-Chem* 201(1):39-44.

Stingley RL, Zou W, Heinze TM, Chen H, Cerniglia CE. 2009. Metabolism of azo dyes by human skin microbiota. *J Med Microbiol* e-pub.

Stone JE, Kissling GE, Lujan SA, Rogozin IB, Stith CM, Burgers PM, Kunkel TA. 2009. Low-fidelity DNA synthesis by the L979F mutator derivative of Saccharomyces cerevisiae DNA polymerase zeta. *Nucleic Acids Res* 37(11):3774-87.

Stout MD, Herbert RA, Kissling GE, Collins BJ, Travlos GS, Witt KL, Melnick RL, Abdo KM, Malarkey DE, Hooth MJ. 2009. Hexavalent chromium is carcinogenic to F344/N rats and B6C3F1 mice after chronic oral exposure. *Environ Health Perspect* 117(5):716-722.

Stout MD, Nyska A, Collins BJ, Witt KL, Kissling GE, Malarkey DE, Hooth MJ. 2009. Chronic toxicity and carcinogenicity studies of chromium picolinate monohydrate administered in feed to F344/N rats and B6C3F1 mice for 2 years. *Food Chem Toxicol* 47(4):729-733.

Streicher RP. 2008. Field evaluation of diacetyl sampling and analytical methods. *J Occup Environ Hyg* 5(11):D111-D116.

Sun J, Lynn BC. 2009. Development of a LC/MS/MS method to analyze butyrylcholinesterase inhibition resulting from multiple pesticide exposure. *J Chromatography B* 877(29):3681-3685.

Sun J, Schnackenberg L, Beger R. 2009. Studies of acetaminophen and metabolites in urine and their correlations with toxicity using metabolomics. *Drug Metabol Lett* 3(3):130-136.

Sun J, Von Tungeln LS, Hines W, Beger RD. 2009. Identification of metabolite profiles of the catechol-O-methyl transferase inhibitor tolcapone in rat urine using LC/MS-based metabonomics analysis. *J Chromatogr B Analyt Technol Biomed Life Sci* 877(24):2557-65.

Swartz CD, Recio L, Green A, Lentz C, Witt KL. 2009. Lack of genotoxicity of three different preparations of aloe barbadensis by the *Salmonella/E. coli* mutagenicity (Ames) assay. *Environ Mol Mutagen* 50(7):567-567.

Tang WY, Newbold R, Mardilovich K, Jefferson W, Cheng RYS, Medvedovic M, Ho SM. 2008. Persistent hypomethylation in the promoter of nucleosomal binding protein 1 (Nsbp1) correlates with overexpression of Nsbp1 in mouse uteri neonatally expose to diethylstilbestrol or genistein. *Endocrin* 149(12):5922-5931.

Tareke E, Heinze TM, Gamboa da Costa G, Ali S. 2009. Acrylamide formed at physiological temperature as a result of asparagine oxidation. *J Agricult Food Chem* 57(20):9730-9733.

Tareke E, Lyn-Cook BA, Duhart HM, Newport, GD, Ali SF. 2009. Acrylamide decreased dopamine levels and increased 3-nitrotyrosine (3-NT) levels in PC-12 cells. *Neurosci Lett* 458(2):89-92.

Thewlis RE, Celik I, Chen BT, Beezhold DH. 2009. Measurement of airborne influenza virus in a hospital emergency department. *Clin Infect Dis* 48(4):438-40.

Thomas M, George NI, Patterson TA, Bowyer JF. 2009. Amphetamine and environmentally induced hyperthermia differentially alter the expression of genes regulating vascular tone and angiogenesis in the meninges and associated vasculature. *Synapse* 63(10):881-894.

Thomas R, Gohlke JM, Stopper GF, Parham FM, Portier CJ. 2009. Choosing the right path: enhancement of biologically relevant sets of genes or proteins using pathway structure. *Genome Biol* 10(4):R44.

Tolleson WH. 2008. Melanin and neuromelanin in the nervous system. In Encyclopedic Reference of *Neuroscience*. 2288-2294.

Tolleson WH. 2009. Renal toxicity of pet foods contaminated with melamine and related compounds. Proceedings of the ACS Symposium on Intentional and Unintentional Contaminants of Food and Feed.

Tong W, Fang H, Mendrick D. 2009. Toxicogenomics and cell-based assays for toxicology. *Interdiscipl Bio Cent J* 1(3):10-15.

Tice RR, Witt KL, Shockley KR, Caspary WJ, Xia M, Huang R, Austin CP. 2009. The use of quantitative high throughput screens (qHTS) in genetic toxicology. *Environ Mol Mutagen* 50(7):542-542.

Tryndyak VP, Beland FA, Pogribny IP. 2009. E-cadherin transcriptional down-regulation by epigenetic and microRNA-200 family alterations is related to mesenchymal and drug-resistant phenotypes in human breast cancer cells. *Int J Cancer* e-pub.

Tryndyak VP, Ross SA, Beland FA, Pogribny IP. 2009. Down-regulation of the microRNAs miR-34a, miR-127, and miR-200b in rat liver during hepatocarcinogenesis induced by a methyl-deficient diet. *Mol Carcinog* 48(6):479-87.

Tucker SP. 2008. Determination of *ortho*-phthalaldehyde in air and on surfaces. *J Environ Monit* 10(11):1337-1349.

Tyurin VA, Tyurina Y, Jung MY, Tungekar MA Wasserloos KJ, Bayir H, Greenberger JS, Kochanek PM, Shvedova AA, Pitt B, Kagan VE. 2009. Mass-spectrometric analysis of hydroperoxy- and hydroxy-derivatives of cardiolipin and phosphatidylserine in cells and tissues induced by pro-apoptotic and pro-inflammatory stimuli. *J Chromatography B-Anal Technol in the Biomed Life Sci* 877(26):2863-2872.

Umbright C, Sellamuthu R, Li S, Kashon M, Luster M, Joseph P. 2009. Blood gene expression markers to detect and distinguish target organ toxicity. *Mol Cell Biochem* 335(1-2):223-34.

van Ommen B, Keijer J, Heil S, Kaput J. 2009. Challenging homeostasis to define biomarkers for nutrition related health. *Mol Nutrition Food Res* 53(7):795-804.

Virji MA, Woskie SR, Waters M, Brueck S, Stancescu D, Gore R, Estill C, Prince M. 2009. Agreement between task-based estimates of the full-shift noise exposure and the full-shift noise dosimetry. *Ann Occup Hyg* 53(3):201-14.

Voltz JW, Card JW, Carey MA, DeGraff LM, Ferguson CD, Flake GP, Bonner JC, Korach KS, Zeldin, DC. 2008. Male sex hormones exacerbate lung function impairment after bleomycin-induced pulmonary fibrosis. *Amer J Respir Cell Mol Biol* 39(1):45-52.

Von Tungeln LS, Churchwell MI, Doerge DR, Shaddock JG, McGarrity LJ, Heflich RH, da Costa GG, Marques MM,Beland FA. 2009. DNA adduct formation and induction of micronuclei and mutations in B6C3F(1)/ Tk mice treated neonatally with acrylamide or glycidamide. *Int J Cancer* 124(9):2006-2015.

Walker NJ, Bucher JR. 2009. A 21st century paradigm for evaluating the health hazards of nanoscale materials? *Toxicol Sci* 110(2):251-4.

Wang JC, Chen T. 2009. Sequencing analysis of mutations induced by *N*-ethyl-*N*-nitrosourea at different sampling times in mouse bone marrow. *J Appl Toxicol* epub.

Wang L, Li Y, Hu P, Teng CT. 2008. PGC-1alpha induces dynamic protein interactions on the ERRalpha gene multi-hormone response element nucleosome in kidney cells. *Biochem J* 416(3):407-19.

Wang L, Li Y, Hu P, Teng CT. 2008. PGC-1alpha induces dynamic protein interactions on the multi-hormone response element nucleosome of ERRalpha gene in kidney cells. *Biochem J Gene* 416:407-419.

Wang J, Sawyer JR, Chen L, Chen T, Honma M, Mei N, Moore M. 2009. The mouse lymphoma assay detects recombination, deletion and aneuploidy. *Toxicol Sci* 109(1):96-105.

Wang SG, Wang L, Yin JJ, Wang Z, Fu PP, Yu HT. 2009. Light-induced toxic effects of tamoxifen: A chemotherapeutic and chemopreventive agent. *J Photochem Photobiol a-Chem* 201(1):50-56.

Wharton SB, O'Callaghan JP, Savva GM, Nicoll JAR, Matthews F, Simpson JE, Forster G, Shaw PJ, Brayne C, Ince PG. 2009. Population variation in glial fibrillary acidic protein levels in brain ageing: relationship to alzheimer-type pathology and dementia. *Dementia Geriatric Cog Disord* 27(5):465-473.

White SS, Birnbaum LS. 2009. An overview of the effects of dioxins and dioxin-like compounds on vertebrates, as documented in human and ecological epidemiology. *J Environ Sci Health C-Environ Carcinog Ecotoxicol Rev* 27(4):197-211.

Wilson RH, Whitehead GS, Nakano H, Free ME, Kolls JK, Cook DN. 2009. Allergic sensitization through the airway prime Th17-dependent neutrophilia and airway hyperresponsiveness. *Am J Respir Crit Care Med* 180(8):720-30.

Wise CK, Kaput J. 2009. A strategy for analyzing gene-nutrient interactions in type 2 diabetes. *J Diabetes Sci Technol* 3(4):710-721.

Witasp E, Shvedova AA, Kagan VE, Fadeel B. 2009. Single-walled carbon nanotubes impair human macrophage engulfment of apoptotic cell corpses. *Inhal Toxicol* 21(S1):131-136.

Witt KL, Malarkey DE, Hobbs CA, Davis JP, Kissling GE, Caspary W, Travlos G,Recio L. 2009. No increases in biomarkers of genetic damage or pathological changes in heart and brain tissues in male rats administered methylphenidate hydrochloride (Ritalin) for 28 days. *Environ Mol Mutagen* 51(1):80-8.

Witt KL, Recio L, Shepard K, Green A, Baldetti C, Winters J, Davis J, Caspary W, Hobbs CA. 2008. Evaluation of micronucleus frequencies and DNA damage in male rats administered methylphenidate hydrochloride (Ritalin) for 28 days. *Environ Mol Mutagen* 49(7):567-567.

Witt KL, Shelby MD, Itchon-Ramos N, Faircloth M, Kissling GE, Chrisman AK, Ravi H, Murli H, Mattison DR and Kollins SH. 2008. Methylphenidate and amphetamine do not induce cytogenetic damage in lymphocytes of children with ADHD. *J Am Acad Child Adolesc Psychiatry* 47(12):1375-83.

Xia QS, Guo L, Dial S, Li Q, Chan PC, Fu PP. 2008. Analysis of gene expression changes of drug metabolizing enzymes in the livers of F344 rats following oral treatment with kava extract. *Chem Research Toxicol* 21(12):41.

Xu H, Heinze TM, Paine DD, Cerniglia CE, Chen H. 2009. Sudan azo dyes and Para Red degradation by prevalent bacteria of the human gastrointestinal tract. *Anaerobe* epub.

Yin JJ, Lao F, Fu PP, Wamer WG, Zhao Y, Wang PC, Qiu Y, Sun B, Xing G, Dong J, Liang XJ, Chen C. 2009. The scavenging of reactive oxygen species and the potential for cell protection by functionalized fullerene materials. *Biomaterials* 30(4):611-21.

Yli Panula E, Fekedulegn DB, Green BJ, Ranta H. 2009. Analysis of airborne Betula pollen in Finland; a 31-year perspective. *Int J Environ Res Public Health* 6(6):1706-1723.

Yoshizawa K, Jelezcova E, Brown AR, Foley JF, Nyska A, Cui X, Hofseth LJ, Maronpot RM, Wilson SH, Sepulveda AR, Sobol RW. 2009. Gastrointestinal hyperplasia with altered expression of DNA polymerase beta. *PLoS One* 4(8):e6493.

Yong LC, Sigurdson AJ, Ward EM, Waters MA, Whelan EA, Petersen MR, Bhatti P, Ramsey MJ, Ron E, Tucker JD. 2009. Increased frequency of chromosome translocations in airline pilots with long-term flying experience. *Occup Environ Med* 66(1):56-62.

Young JF, Luecke R, Pearce BA, Lee T, Ahn H, Baek S, Moon H, Dye DW, Davis TM, Taylor SH. 2009. Human organ/tissue growth algorithms that include obese individuals and black/white population organ weight similarities from autopsy data. *J Toxicology Environ Health Part A* 72(8):527-40.

Young SH, Antonini JM, Roberts JR. 2008. Single pre-exposure to a high dose of zymosan enhances lung defense mechanisms and accelerates the pulmonary clearance of a bacterial pathogen in rats. *Exp Lung Res* 34(9):559-578.

Young SH, Antonini JM, Roberts JR. 2009. Preexposure to repeated low doses of zymosan increases the susceptibility to pulmonary infection in rats. *Exp Lung Res* 35(7):570-90.

Zegre Cannon C, Godfrey VL, King-Herbert A, Nielsen JN. 2009. Metastatic uterine adenocarcinoma in an 8-year-old Gilt. *JAALAS* 48(6):795-800.

Zegre-Cannon C, Waxer D, Myers P, Clark J, Goulding DR, King-Herbert AP, Blankenship-Paris T. 2009. Evaluation of route of administration and dosage of tramadol as an analgesic in the rat. *J Amer Assoc Lab Animal Sci* 48(5):564-564.

Zhang X, Paule MG. 2009. Neurotoxicant-induced animal models of neurological disorders. In *In Vivo* Systems: Animal Models of Neurological Diseases.

Zhang X, Paule MG, Newport GD, Zou X, Sadovova N, Berridge MS, Apana SM, Hanig JP, Slikker W Jr, Wang C. 2009. A minimally invasive, translational biomarker of ketamine-induced neuronal death in rats: microPET Imaging using 18F-annexin V. *Toxicol Sci* 111(2):355-61.

Zhang XD, Hubbs AF, Siegel PD. 2009. Changes in asthma-like responses after extended removal from exposure to trimellitic anhydride in the Brown Norway rat model. *Clin Exp Allergy* 39(11):1746-53.

Zhang Y, Rivera Rosado LA, Moon SY, Zhang B. 2009. Silencing of D4-GDI inhibits growth and invasive behavior in MDA-MB-231 cells by activation of Rac-dependent p38 and JNK signaling. *J Biol Chem* 284(19):12956-65.

Zhang YD, Beezhold K, Castranova V, Shi XL, Chen F. 2009. Characterization of an alternatively spliced GADD45 alpha, GADD45 alpha 1 Isoform, in arsenic-treated epithelial cells. *Mol Carcinogen* 48(5):454-464.

Zhang YF, El-Sikhry H, Chaudhary KR, Batchu SN, Shayeganpour A, Jukar TO, Bradbury JA, Graves JP, DeGraff LM, Myers P, Rouse DC, Foley J, Nyska A, Zeldin DC, Seubert JM. 2009. Overexpression of CYP2J2 provides protection against doxorubicin-induced cardiotoxicity. *Amer J Physiol-Heart Cir Physiol* 297(1):H37-H46.

Zhao H, Ma JK, Barger MW, Mercer RR, Millecchia L, Schwegler-Berry D, Castranova V, Ma JY. 2009. Reactive oxygen species- and nitric oxide-mediated lung inflammation and mitochondrial dysfunction in wild-type and iNOS-deficient mice exposed to diesel exhaust particles. *J Toxicol Environ Health* A 72(8):560-70.

Zhao J, Bowman L, Zhang X, Shi X, Jiang B, Castranova V, Ding M. 2009. Metallic nickel nano- and fine particles induce JB6 cell apoptosis through a caspase-8/AIF mediated cytochrome c-independent pathway. *J Nanobiotechnology* 7:2.

Zheng HL, Wang ZX, Shi XQ, Wang ZZ. 2009. XRCC1 polymorphisms and lung cancer risk in Chinese populations: A meta-analysis. *Lung Cancer* 65(3):268-273.

Zhu J, Xu W, Wang J, Ali SF, Angulo J. 2009. The neurokinin-1 receptor modulates the methamphetamine-induced striatal apoptosis and nitric oxide formation in mice. *J Neurochem* 111:656-668.

Zou W, Cerniglia CE, Chen H. 2009. Azoreductase in Staphylococcus aureus. Current Protocols in Toxicology.

Zou W, Frye JG, Chang C, Liu J, Cerniglia CE, Nayak RR. 2009. Microarray analysis of antimicrobial-resistance genes in *Salmonella* enterica from preharvest poultry environment. *J Appl Microbiol* 107(3):906-914.

Zou X, Patterson TA, Divine RL, Sadovova N, Zhang X, Hanig JP, Paule MG, Slikker W, Jr, Wang C. 2009. Prolonged exposure to ketamine increases neurodegeneration in the developing monkey brain. *Int J Dev Neurosci* 27(7):727-31.

Zou X, Patterson TA, Sadovova N, Twaddle NC, Doerge DR, Zhang X, Fu X, Hanig JP, Paule MG, Slikker W, Wang C. 2009. Potential neurotoxicity of ketamine in the developing rat rain. *Toxicol Sci* 108(1):149-58.

Notes

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